ON THE PRESENTATION AND RELEVANCE OF LATERALITY: A STUDY OF PSYCHOSIS

By

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Thesis submitted to the University of Nottingham for the degree of Doctor of Medicine

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TITLE:
On the Presentation and Relevance of Laterality: A Study of Psychosis

SUBTITLE:
Exploring the concepts that associate handedness, lateralization of function and psychosis in two UK birth cohorts.

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DEGREE:
Doctorate of Medicine (DM)

UNIVERSITY:
University of Nottingham

DIVISION:
Psychiatry and Community Mental Health

SUBMITTED TO:
Faculty of Medicine, University of Nottingham

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A CDROM accompanies this manuscript. The 3D figures in chapters 8 and 9 are quite complex, and it is recommended that these are examined by the reader in 3D, in order to fully appreciate their shapes. The CDROM contains the figures as VRML v1.0 models, and a compact viewer.

Abstract

A discussion of concepts of lateralization and handedness is followed by an examination of the three-way relationships between lateralization of brain function, level of function, and schizophrenia. It is proposed that conventional examinations of such relationships, using lateralization indices, can be unenlightening or even misleading, and that alternative approaches are preferable.

Support for this thesis is sought in analyses of data from two UK national birth cohorts. The author's process of gathering data on psychiatric outcomes is presented in detail. Previously-published findings in this data, employing laterality indices, are presented and their shortcomings discussed.

Several alternative approaches to examining the relationships between measures of functional lateralization and level of function are developed, including a novel application of the method of principal curves, and a three-dimensional presentation of function as height over a 'laterality surface'. This latter approach is applied to a number of measures of function in the cohort datasets, including measures of cognitive ability, social success and psychiatric illness, including schizophrenia. The benefits of this method of presentation over previously-published presentations are discussed in the context of several contemporary hypotheses that touch upon the relationships between functional lateralization, cognitive function and schizophrenia.

Preface

Statement of Authorship

The discussion on the nature of lateralization, the critique of how it has been quantified in the past and how it may be quantified without recourse to indices, how the measure relates to central and peripheral functions, and how this might be associated with outcome have emerged from numerous discussions of these topics with colleagues and associates since 1996. Their synthesis is my own work.

The 1958 National Child Development Study (NCDS) is a large general population birth cohort that has been followed continuously since its inception in 1958. The 1970 British Births cohort study (BCS70) is a similar study. The databases on the two birth cohorts that are drawn on are the work of thousands of individuals over many decades. Their origins, constitution, and data used in this thesis are described in chapter 5.

An identification of individuals in these cohorts with schizophrenia was initially undertaken in the NCDS cohort alone in the mid-1980's by Dr John Done, Professor Tim Crow and Professor Eve Johnston. A repeat of the exercise of case identification, in order to increase numbers of cases of schizophrenia to allow for analyses of sex differences, was planned in the early 1990's. Between 1995 and 1997, under the supervision of Drs Crow & Done I developed a database of admissions, pursued those regionally-held lists of psychiatric admissions not yet obtained by Dr Done, and then obtained casenotes of the individuals on these lists. I examined the notes to obtain clinical data and entered these into the OPCRIT computerised multi-classification diagnostic programme for psychosis. I also used the casenotes to derive 'clinical' DSMIV diagnoses in a parallel effort with Dr Mike Blows, each blind to the others' diagnoses. Differences were then resolved in a three-way discussion between Dr Blows, Dr Crow and myself. This process is documented in chapter 6.

In the first paper in chapter 7 I was responsible for a series of exploratory analyses of the data using a variety of techniques, before producing the lowess analysis (figure 3). This was felt to most succinctly and clearly demonstrate the relationships between sex, performance and laterality, which were more difficult to grasp in the 'by bins' figure (figure 2), where the dip is off to one side (by virtue of the group sampling employed).

The 'discovery' of the misinterpretation of laterality index data described in the second paper in chapter 7 was mine, Tim Crow providing a valuable sounding-board on the implications of the corrected findings. The development and application of the relatively novel two- and three-dimensional data analysis and presentation techniques in chapters 8 and 9 is mine.

Acknowledgements

My thanks go to Tim Crow and John Done, without whose help and encouragement I would not have undertaken the casefinding, nor developed an interest in demonstrating associations between psychological function and measures of right-left difference. I also thank Peter Jones, whose helpful and supportive comments and insights kept this manuscript on track.
I am grateful to Peter Shepherd at City University for his support for the use of the cohort datasets, to Dr Tim Croudace, Dr Bert Park and Professor Ian Dryden at Nottingham University for statistical advice, Chinlyn U at Nottingham University and Dr Walter Barker at the University of Bristol for advice on the use of BCS70 data, and Dr John Coulthard at the University of British Columbia for support with VRML. Dr Catherine Gordon and Dr Bert Park read draft versions of this thesis and suggested improvements. All remaining errors are mine.

Introduction

What does handedness have to do with psychiatry?

One of the influential notions in the field of research into psychosis aetiology over the last 20 years has been Tim Crow's hypothesis that psychotic illness occurs at the point of 'hemispheric indecision'. It was during attempts to investigate this phenomenon that it was discovered that methods commonly employed to present such laterality data were flawed, and that fundamental issues relating to the distribution of lateralization required clarification. The work presented in this thesis consists for the most part of an exploration of these issues, and the seeking out of methods that might resolve these. These new methods are then re-applied to laterality measures in psychosis, to see whether any new light is shed on the field.

The main area under consideration can be conceptualised in terms of figure 1; each association is reviewed in chapter 3, but what is chiefly under consideration are the conceptual uncertainties in the apex of the figure, and ultimately how these influence observations of association opposite.

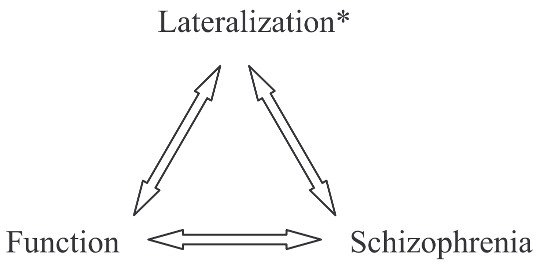


Figure 1: A Triangle of associations

*The spelling lateralize, lateralization etc. is used throughout, as 'lateral' is of Latin, and not French origin. While those words of French origin ending in –ise retain the s, for all others the Greek ending -ize is correct, notwithstanding either use being generally acceptable.

The human brain has two superficially similar halves, and appears to be 'wired up' as a huge network of neurons. If we think of the brain in this way, it suggests that any function it wishes to perform could be carried out by any part of this network. Studies of brain-damaged individuals strongly suggest that when some areas specialized to given tasks are destroyed, some if not all of their function can be taken up by other brain areas. Exactly how the brain parcels up the tasks of daily living, where it performs what, has a potential for variation between individuals.

As well as functional specialization, there is also structural specialization within the brain. From specific lobes and tracts of 'wiring bundles', to the finest details of cellular ultrastructure, the brain shows an enormous variety of specialization. It is hard to imagine this specialization is not a consequence of selective pressures to improve brain function.

So there is a tension – the brain is hugely interconnected in a manner best modeled by repeated units of generalized function, and on the other hand there is a degree of consistency between brains, in patterns of specialization seen in specific areas. A synthesis is needed to understand how such anonymous generality and such anatomical specificity combine.

In a generalised network, the notion of a task being performed better or worse depending on where (and to what extent) it is localized, is illuminated by what we see around us. Small working-groups get on with tasks better than over-worked individuals or sprawling committees; manufacturing industry does better if design decisions are made closer to the shop floor. Computers function more efficiently when they can pass parts of a task to a specialised sub-processor. Thus a plastic system will interact with external and internal constraints (degrees of autonomy, the need for information, propagation delays and so forth) to arrive at an optimum degree of localisation for a given task in a given circumstance. Thus one can conceptualise the 'cybernetics' of a system, the relationship between performance and this rather abstract parameter of 'localisation'. And the human brain does appear to localise function in this way. And there is variation in the population, measurable by peripheral tests and central imaging.

And yet despite this variation, brain function is remarkably consistent; there are few if any functions of daily living, functions that define us as human, that even the dullest member of society cannot carry out. Outside the MENSA camp of abstract tasks with dubious ethological validity, ‘intelligence’ is much more readily defined in terms of that which we all can do, than in terms that distinguish normal individuals. And the chief means by which we monitor, discuss, plan and record these activities is through the use of abstract language, a facility that seems absent in other species. Abstract language function, almost by definition, might be the highest expression of human brain function.

It would seem very odd if there were no evidence at all that this 'highest' function were unaffected by its degree of localisation in the brain.

The possibilities for variation are such that any systematic relationship between a measure of localisation of function and that function, can be lost in 'noise'. In this thesis, individual-level data in a whole-population cohort is used largely for the reason that by analysing a large number of data points we have a better chance of detecting a weak signal through such noise.

Population studies employ indirect measures of localisation of function in order to keep data-gathering manageable, and this thesis uses a measure of hand skill as a proxy measure of functional localisation, or lateralization of function to one hemisphere or the other. A wide variety of such measures have been employed over the years, and they tend to correlate poorly. There isn’t a key underlying variable of lateralization, or rather, we lack sufficient understanding of how the brain works to determine, from the many noisy measurements we can make, which one it might be. This is a big leap, from localisation of processing in a network to lateralization of brain function measured by hand skill. Hand skill is used in the absence of a better measure.

Straightforward questions may be asked using these measures. Is level of brain function associated with degree of localisation of brain function? How is “degree of localisation” distributed in the population? Is the variation one that impacts on an individual’s life-course ie. does it impact upon 'real-world' psychological functioning, to affect outcome measures such as success in life, or even clinical psychiatric illnesses?

If it did, we might then be justified in speculating about the relationship between level of brain function and degree of localisation of that function in quantitative terms: How does brain function vary with this basic parameter?

Structured summary

Chapter 1: Symmetry, asymmetry and lateralization
- An examination of what is meant by symmetry, asymmetry and laterality
- How 'laterality' is conceptualised and measured
- Examples from nature, from physics to neuroscience, structural and functional
- A discussion of the potential costs and benefits of lateralising function

Chapter 2: Measuring handedness
- Why measure handedness?
- How handedness may be conceptualised and measured
- Some problems with how laterality is conceptualised, measured and analysed

Chapter 3: Lateralization, outcome and psychosis
- A brief 'history of handedness', including associations between laterality and cognitive function
- Theories of aetiology, including recent genetic theories
- A brief 'history of psychosis', including associations between psychosis, cognitive function and laterality
- Theories of aetiology, including the neurodevelopmental hypothesis, and the Crow hypothesis
- Predictions from these theories about the association between handedness, laterality and cognitive function

Chapter 4: The thesis
- A statement of the thesis, including where it lies on a 'map' of laterality research

Chapter 5: The UK NCDS & BCS70 national birth cohorts
- Why cohort data has been used to examine this question
- A brief description of the cohorts, and the data used for analysis

Chapter 6: Psychiatric casefinding in cohort data
- A description of the process of gathering psychiatric cases in the birth cohorts, carried out between 1995-98 by the author
- The results of this process, with a consideration of sampling biases and the effects of attrition

Chapter 7: The 'distal & proximal phenotypes'
- Paper 1: A paper disclosing an association between functional asymmetry and cognitive function, and a critique of the finding
- Paper 2: A paper that uncovers an error in interpreting laterality data in previous literature, and the findings if this error is avoided

Chapter 8: Cognitive function and hand skill difference - comparing findings between tasks and cohorts
- A novel analysis of the association between cognitive function and laterality indices, in two measures and in two cohorts
- An improved and extended analysis of the type in paper 2, chapter 7

- Level of function and lateralization without laterality indices: lateralization is good for you!

Chapter 9: Psychological outcomes and hand skill differences
- Relationships between asymmetry and adult success
- Relationships between asymmetry and psychiatric illness

Chapter 10: General discussion
- A summary of the findings
- A discussion of their significance
- Future work

Chapter 1: Lateralization: perturbing symmetry

Introduction - Adventures in Flatland.

"To
The Inhabitants of SPACE IN GENERAL
And H. C. IN PARTICULAR
This Work is Dedicated
By a Humble Native of Flatland
In the Hope that
Even as he was Initiated into the Mysteries
Of THREE Dimensions
Having been previously conversant
With ONLY TWO
So the Citizens of that Celestial Region
May aspire yet higher and higher
To the Secrets of FOUR FIVE OR EVEN SIX Dimensions
Thereby contributing
To the Enlargement of THE IMAGINATION
And the possible Development
Of that most rare and excellent Gift of MODESTY
Among the Superior Races
Of SOLID HUMANITY"

Edwin Abbot's exposition of the paradoxes associated with consciously existing in one order of dimensionality while considering another, still provides wry commentary on the pitfalls awaiting all who research into laterality (Abbot 1884). The suggestion that 'enlargement of the imagination' should be allied to 'development of... modesty' is timely, in a field that initially appears benign, mature and well-ordered, but whose undergrowth soon trips the unwary traveller.

His story is of a 2-dimensional being, a square, living in a 2-dimensional world, whose worldview is one day revolutionised when he is dragged into a third, unknown dimension by a 3-dimensional being. Our hero's perspective is at once changed for ever. Matters that appeared contradictory and confusing in two dimensions become self-explanatory in three. The breakthrough, however, is not a simple of triumph of three dimensions over two, rather the realisation that nature can be formulated in as many dimensions as might be useful.

Abbot's humility is a good place to start an examination of handedness, as more than a century of research has left the field awash with inconsistencies and contradictions, from the basic conceptualisation of the properties involved, through measurement of these properties and traps in their interpretation.

In part these arise from a lack of a comprehensive model of brain function. While this would provide an ideal framework for understanding lateralization of function, it may remain an unattainable dream. Our consciousness, perhaps merely an artefact of neural processes contributing to our survival (Carpenter 1984 p.316), may be too much a subset of brain function. We may lack sufficient intelligence to truly appreciate our own intelligence; ask a clock how it works, and all it will tell you is the time.

Further, the nature of conscious experience is of a linear flow of events, 'time', reflected in the qualities of rational discourse and the linear ribbon of sound with which we communicate, speech. Thus our conscious, 'thinking' experience of the world tends to be focussed on one thing at a time, otherwise we feel a sense of being overwhelmed. Appreciating two things simultaneously eg. events on one side and another, is a challenge, and the analytical processes of data reduction that subliminally kick in to help us deal with this simultaneity, can prematurely confound our attempts to really understand what is going on.

There may be more mundane reasons why the field is convoluted. However, before I seem to claim any new revelations in this thesis, I am also warned by Abbot's tale. His hero challenges the prevailing orthodoxy, and is rewarded with incarceration. Anyone claiming special revelation about the physical world needs the diplomatic skill of putting their foot down while avoiding treading on anyone's toes. For example, readers interested in the historical background of current thinking on 'what' functions have been located in different brain areas over the years and 'why', are directed to Anne Harrington's treatise on this subject (Harrington 1989). This thesis concentrates much more on 'how' functional differences by side are measured, and the differences conceptualised.

In this chapter we shall examine
- what is meant by 'symmetry' and 'asymmetry', and how these words relate to notions of 'laterality' and 'lateralization'
- the different 'types' of asymmetry we see in the natural world, noting how lateralization is conceptualised
- the numerous types of measurement we can consider with regard to brain lateralization
- theoretical advantages or disadvantages to an organism of being more or less symmetrical, and function being more or less localised.

WHAT IS SYMMETRY?

"Symmetry (noun)
1 a) correct proportion of the parts of a thing; balance, harmony. b) beauty resulting from this.
2 a) a structure that allows an object to be divided into parts of an equal shape and size and similar position to the point or line or plane of division. b) the possession of such a structure. c) approximation to such a structure."
(Concise Oxford Dictionary 1999)

Symmetry is an appreciation of the world, an impression, but it is also the result of an analysis. The analysis is that the object under consideration consists of parts of equal size, shape and position with reference to a point or line. Invariably each part appears to consist of a reflection of the other parts about this point or line.

It might be thought to suggest a process of development, bilateral similarity of conditions for that development, whether it is the symmetrical properties of spinning subatomic particles, a crystal lattice, a protein sheet, or an organism. However, symmetry is primarily an impression about an object. An object's apparent bilateral symmetry may tell us nothing about its origins; the two 'halves' may be independent of each other, the symmetry existing solely in the eye of the beholder (Figure 1).

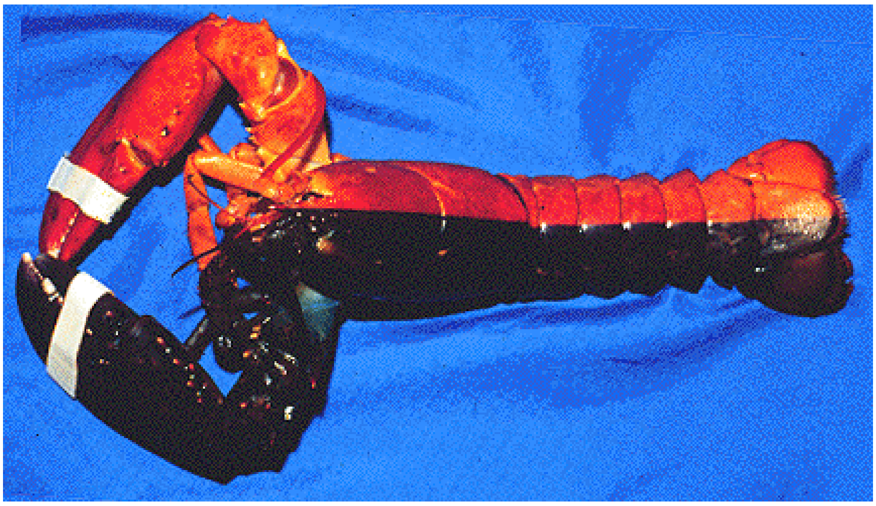


Fig 1. A lobster - midline symmetry. Or not?
Such colouring suggests this is a gynandromorph hermaphrodite - female on one side and male on the other. At the time of writing, this specimen was alive and well.
(Picture courtesy of Geoff Ralling, ©1996 Graphic Design Dept., University of Prince Edward Island)

One could consider bilateral symmetry in a 'low order' of unidimensionality. However, the retina is essentially a two-dimensional sense organ, and information from this is most readily appreciated as a two-dimensional image. Without a second dimension, width, unidimensional objects are difficult to appreciate. Similarly, symmetry in 3 dimensions is more abstract than in 2. Although higher and lower orders of dimensional symmetry are present in nature, the most readily-appreciated symmetry seems to be that about a straight line on a 2D plane. Although fractal geometry reminds us that symmetry can exist on many levels, in any system subject to entropy order is decreasing, and higher orders of symmetry will be numerically rarer than lower. For these and no doubt other reasons, we appreciate symmetry in two dimensions, and especially bilateral symmetry, more readily than higher or lower orders.

Links between bilaterality and direction set in early; you summarise a symmetrical object by only having to describe half of it, then say 'the rest is the same, only in the opposite direction'. Hence bilateral is an adjective which reduces the information required to describe an object. Encountering innumerable different objects in daily life, reflection is used as an initial step in this data reduction. The fact that this analysis is done very early on in the progression of information from the eye to the "conscious cortex" is reflected by implementation of this step of image analysis early on in the pathways from optic nerve to cortex. It is similar in some ways to the concept of 'colour', which to the brain is not so much a description of wavelength of light, but rather an intrinsic quality of a surface that is constant regardless of the intensity of ambient light (Carpenter 1984 p.180). Bilaterality, a description of an object involving a reflection across a midline, is object-constant, especially as real objects cannot reflect, only translate and rotate.

The next step in describing the object is to delineate the ways in which the two halves differ. If the object is felt to display symmetry, this should be quicker than defining each half! Notions of 'laterality' start to intrude here, as a way of describing differences between two sides. Let us note at this point that the halves are still only nominally 'reflections' of each other.

WHAT IS ASYMMETRY?

'There's glory for you!'
`I don't know what you mean by "glory,"' Alice said.
Humpty Dumpty smiled contemptuously. `Of course you don't - till I tell you. I meant "there's a nice knock-down argument for you!"'
`But "glory" doesn't mean "a nice knock-down argument,"' Alice objected.
`When I use a word,' Humpty Dumpty said in rather a scornful tone, `it means just what I choose it to mean - neither more nor less.'
`The question is,' said Alice, `whether you CAN make words mean so many different things.'
`The question is,' said Humpty Dumpty, `which is to be master - that's all.'"

from "Through the Looking Glass" by Lewis Carrol

"Asymmetry (noun):

1 lack of symmetry.
2 an instance of this"
(Concise Oxford Dictionary 1999)

This seems straightforward enough.

However, laterality and lateralization follow, as words used to describe a 'degree of asymmetry' in the distribution of a function or structure. There is clearly a problem; when one speaks of ‘asymmetry’ this is a very general term, whereas 'laterality' and 'lateralization' sound much more specific. A noun and a verb derived from the word ‘lateral’ (Latin 'lateralis' from latus lateris ‘side’), they immediately conjure up suggestions of bilateral partitioning of some form or action, describing a deviation from symmetry along a single axis. Thus, although 'lateralization' can seem a straightforward concept, complicated merely by the vagaries of statistical analysis, it might actually propose any one of a fairly specific group of models of deviation from symmetry.

In the absence of a hypothesis of how the deviations from symmetry arose, this conceptualisation of any such deviations may simply be inappropriate or irrelevant to the processes under study. However, nothing is there to stop one making measurements and performing calculations, and believing one is studying something. We need to be very careful to avoid putting the cart before the horse, if we are to avoid Humpty Dumpty's "glory" for us all.

WHAT TYPES OF ASYMMETRY DO WE SEE IN NATURE?

There are many different ways of measuring asymmetry - writing hand used, position of activation on a fMRI scan, rotation of a protein etc. These different measures make a number of assumptions about what is measured.

There are three concepts of lateralization in common use:

1. A binary, all-or nothing choice
- preferred hand at a given task
- side of injection that abolishes speech in the Wada test etc.

2. A probabilistic continuum derived from multiple binary measures
- "90% of people write with their left hand"
- "90% of children under 4/12 roll to the right >50% of the time".

3. A continuous variability of lateralization
- deviation of a midline structure
- some function of two continuous measures on either side.

However, these clusters of observation types can still group data from wildly different conceptual viewpoints. For example, Edinburgh Handedness Inventory data from a group of lefthanders (a nominally continuous score) might be compared with data on structural midline deviations. Yet the former might alternatively be conceived as a probabilistic continuum of values in a population deriving from absolute categories, and the latter as noisily linked to just one of those preferences. So the analysis risks tremendous confounding and loss of power, despite the fact that both measures look convincing. Just establishing a correlation does not advance things very far.

On examination, these three clusters of conceptual and measurement possibilities break further, into a number of categories along a number of different measurement dimensions.
(See Appendix A for numbered notes on examples).

1. The number of measures involved :1, 2, 3, ... N

A single measure

- Particles and anti-particles, and neutrinos only exist (in this universe) with 'left-handed' (clockwise) spin [(1)]
- chiral proteins [(2)]
- chiral helices [(3)]
- rotation of unicellular ciliates [(4)]
- arrangement of asymmetries in invertebrates [(5)]
- vertebrate asymmetries (cf. situs invertus) [(6)]
- some 'multiple measures' may actually be 'linked asymmetries' [(7)]
- 'Which hand is most commonly used for writing?".

Two measures - "Performance at a task by right hand, and performance by left hand".
Many measures - "Hand preferred for writing / sewing / unscrewing etc.".

2. The number and type of categories conceptualised :1, 2, 3, ... N

How the categories are conceptualised is central to any theory about their origins, or response to environment.
'No category' - the concept may be that the original state from which organisms vary is random asymmetry [8].
One category - no variability beyond random fluctuation.
Two categories - preferred claw for crushing in lobsters [9].
Many categories - a neural network model.

If there are enough categories on a ratio scale, variability might be conceptualised as a centre of activity, like a 'mean' displacement from the midline, and its distribution, like a 'standard deviation', for a given task.

3. The number of categories measured :2, 3, 4, ... N
Two categories - Right or left-handed.
Three categories - Right hand preferred, Either, or Left.
Many categories - continuous measure eg. of angle of deviation of a midline structure, angle of 'changeover' in 'moving pegboard'-style tests.

Each of these are conceptually-distinct - if three categories are measured in one experimental setting, and two in another, we cannot say how the three categories in the first case compare with the two in the second, or vice-versa. Although seemingly very similar measures, they are not strictly comparable.

4. The noise considered to affect the measure :Zero to a lot
Little noise - preferred hand for writing.
Lots of noise
- fluctuating asymmetries
- results of Wada test.

The presumed presence of noise is addressed with multiple measures, which can be analysed to give a 'probabilistic' continuum of results in a population of individuals. Conceptually distinct from a continuum of results derived from continuous measures in a population.

5. The 'axis' on which the noise is acting
- noise in the expression of a trait eg. recall error, recall bias, environmental biases (eg. scissor usage)
- noise in the measurement of a trait eg. recording uncertainty or error
- noise in the development of a trait (fluctuating asymmetries [10])
- 'noise' due to practice or fatigue effects over repeated tests (see Chapter 2).

Many measures of brain lateralization and localisation assume there to be a lot of 'noise' - individual-level variation that is apparently stochastic and otherwise uninformative eg. that found in dichotic listening or fMRI data. Some handedness theories account for all variation beyond two underlying categories in this manner (see McManus theory, chapter 3).

These axes are useful in sorting out the ways in which measures of brain structure and function might differ. If there is a sense in which they are all proxy measures of the same thing, one can then be explicit about how they relate, rather than just assuming that they are comparable because they've resulted in similar-looking measures eg. laterality indices.

The individual-level variation is at least in part due to random variation or 'noise'. One consequence of this is that measures in individuals can be seen as merely uncertain indicators of whatever may be underlying the laterality, and measures in populations will for the most part reflect noise, and appear normally-distributed to a first approximation. The relationship between how a factor varies in an individual and how it will then vary a population may remain obscure. However, this is in stark contrast to the clear asymmetry of the distribution of handedness. I am uncertain how to resolve this issue.

Brain asymmetry - structural & functional, proximal & distal

Asymmetries can develop from the earliest moments of embryonic morphological definition. The neural crest develops on the lips of the midline neural tube, and gives rise to a wide variety of important features, neural and non-neural, in the developing foetus. Any interference with neural crest cells embryonically can produce effects in the areas they end up in. Even experimental interference with embryonic neural crest cells can lead to anomalies in asymmetrical structures eg. transposition of the great vessels (Geschwind & Galaburda 1987 Chap 15).

There is evidence of cerebral asymmetry in reptiles, amphibians, fishes, birds, mammals and non-human primates. These asymmetries probably demonstrate population biases as well eg. some singing birds show an enlarged left-sided nucleus largely responsible for the dawn chorus, mother mice show a left specialisation for distinguishing newborn cries, and a dolphin has demonstrated left-superiority for learning gestures (Galaburda 1985).

Overall, lateralization of language function to the left hemisphere is found in many species. Although the functional paradigms employed to determine this in non-human species lack facilities for easy observation in large numbers of subjects, it seems likely that many of these cerebral functional asymmetries are maintained at population-level. Man's nearest relative, the chimpanzee has demonstrated left-hemisphere advantage for understanding plastic symbols that have literal meanings (for reviews see Corballis 1991, pp 182-185, Bradshaw & Rogers 1993).

The human brain, while superficially symmetrical, displays important anatomical asymmetries. Despite the observations by Broca (1861) & Dax (1865) in the 19th century that human speech function was in some way crucially located in the left hemisphere, the general consensus was until comparatively recently that this was not accompanied by any significant structural difference between the two halves of the brain (von Bonin 1962).

However, there *are* structural asymmetries to the human brain. The first to be reported in a consistent series was that of the planum temporale, part of the temporal lobe, noted to be on average one third longer on the left in 65%, and on the right in 11% of brains by Geschwind & Levitsky in 1968. Following this report, attitudes changed and a variety of consistent structural asymmetries were noted, in some cases 'rehabilitated' eg. the Sylvian fissure being longer on the left (Cunningham 1892!). As well as differences in particular regions, overall differences in sizes of lobes has been found, the frontal lobe being wider on R and the occipital lobe wider on L (Galaburda et al 1978). These larger-scale assessments can be interpreted that the brain is 'rotated' somewhat about a vertical axis, sometimes referred to as a notional rotation or "torque".

What is important to note at this stage is that these are actually bivariate measures - two continuous measures, one on each side, conceptually quite distinct from categorical measures. They can be interpreted as a single categorical measure with two categories (larger on left or right), but are originally bivariate.

Functional asymmetries

These involve all asymmetries in which the focus is the activity, rather than the anatomy. These are therefore all comparisons of a measure on one side which is compared to the other: bivariate, continuous measures.

'Proximal' functional asymmetries

['Proximal', asymmetry of function in the brain, in contrast to 'Distal', asymmetry of function in the limbs]

In 1836, a doctor named Marc Dax presented a case series of patients with speech loss following brain injury, to a small audience at a medical society in Montpelier, France, (Dax 1865). He observed that in all of them, the damage was to the left side of the brain alone. This observation, made famous by Paul Broca almost 30 years later (who pipped Dax at posterity's post by publishing first) marked an important step in conceptualising brain functions as taking place in specific brain areas (Broca 1861). Broca identified the area crucial to speech production as the posterior portion of the third convolution of the brain, just forward of the motor cortex responsible for mouth movements. In his series too, lesions accompanied by speech loss were left-sided. He next suggested that the left hemisphere was 'dominant' for language, and went further to suggest that in left-handers the right hemisphere would be dominant (Broca 1865).

The latter 'Broca's rule' has fallen into disrepute, as the correlation between hand preference and speech dominance side has proved to be far from perfect. Indeed, footedness correlates more closely with side for language dominance than handedness (Elias & Bryden 1998). Left-sided speech generation is the commonest in humans (Rasmussen & Milner 1974), but we are not alone in localising speech production to the left hemisphere (see above).

Exploring proximal asymmetries

- Brain damaged subjects
Observations of brain-damaged patients may merely confuse the field. The area damaged may contain nerve tracts (ie. 'wiring bundles') vital to speech, whereas the processing per se occurs elsewhere. Also, these are brains that have been damaged.

We can only infer, not know, that under normal circumstances the speech production occurs in this area.

- The Wada test

The cerebral hemisphere 'dominant' for language (ie. the half of the brain that does the talking) can be determined by the Wada test (Wada and Rasmussen 1960), in which an anaesthetic, sodium amytal, is injected into the carotid artery on one side of the brain, then the other. For about 10 minutes after injection, motor and sensory control are lost on the contralateral side. When injected on the 'dominant' side, speech ceases, then returns, initially laced with errors, whereas injection on the non-dominant side merely causes a brief interruption of speech immediately after injection. That this is a reversible test is undeniable, and the observation shakes the 'vital bundle' theory above. However, data from such experiments concerns individuals who are undergoing neurosurgery for intractable epilepsy, where neuropsychological testing has suggested 'atypical' (ie. right-side) speech dominance. The Wada test is performed to determine whether surgical removal of the temporal lobe will also remove expressive speech. Thus the findings from this test may not generalise, as the brains being tested are already abnormal.

Conceptually, this is a 2-category categorical measure, with little 'noise' (and only performed once in most individuals anyway).

- 'Split-brain' patients

Findings in patients with brain damage have since the 1960's been added to by studies of so-called 'split brain' patients. Here the corpus callosum has been surgically divided, usually to treat intractable epilepsy, thus disconnecting the two halves of the brain. By presenting images and stimuli to appropriate fields of view, one can present them to one half of the brain or the other. Findings suggest that the right side of the brain is superior at performing tasks involving interpretation and manipulation of spatial information. The anatomical localisation of such processing is less precise, resonating with the impression that the right side of the brain is involved more in connectionist, highly parallel processes, in contrast to more localised, linear processes on the left side. Thus there is evidence that the right side of the brain 'deals with' spatial processing, music appreciation and interpretation of emotional information, and the left side with the expression of specifics ('praxis'), such as language production (see brief review in Corballis 1991 p.247-275). Thus the concept of cerebral dominance is not an expression of absolute superiority, rather merely an establishment of which side of the brain is producing speech, once more a 2-category categorical measure with little 'noise'.

- Dichotic listening

Another paradigm for establishing cerebral 'dominance' is Kimura's dichotic listening test (Kimura 1961). Epileptic patients with headphones on were supplied simultaneously with a different message (eg. a three number code) to each ear. Kimura found a slight superiority of recall of the right-ear messages. Conversely, individuals with right-hemisphere speech (by the Wada test) showed a superiority of recall of the left ear messages. Thus messages were perceived (by the speech-dominant hemisphere) when presented to the opposite ear.

The explanation is as follows:
- Each ear projects to both hemispheres
- The pathway that crosses to the contralateral hemisphere is 'stronger' than the shorter path to the ipsilateral hemisphere.
- So, if a stimulus is supplied to one ear only, it goes directly to both hemispheres
- If different stimuli are presented to each ear, the 'crossed' pathway is stronger, so the stimulus heard is the one that crosses to the 'dominant' hemisphere.

A similar test involves flashing words & images to the left and right visual fields, too quickly to allow the eye to move and place the target centrally on the retina. Again, visual recall is superior for items presented to the side dominant for speech, in this instance the opposite visual field.

There is therefore a significant correlation between side of ear advantage and visual field advantage on such dichotic testing and the other side of the brain for speech dominance. However, the effect size is not large, and the variance such that in individuals, side of 'advantage' may reverse on re-testing, and visual hemifield and dichotic listening results can contradict each other. The results are noisy, in part because of the sensitivity of both tests to testing conditions and individual differences in thresholds etc. Finally, although the sign of the result may appear straightforward to interpret, the meaning of the magnitude is less clear.

This measure is of multiple 2-category measures in an individual, with a lot of noise.

Such testing can be further sub-divided into tests of more specific task-processing than simple recognition and recall. These multi-measure tests produce a mixture of categorical and continuous measures which remain 'noisy' (Boles 1991).

Other cerebral functions have been localised, such as the location of areas of sensory and motor cortex servicing the appropriate areas. However, how localisation restricts key aspects of function to one hemisphere, for functions that are of themselves not anatomically lateralized eg. spatial awareness, remains at this time the subject of much speculation (see review by Hugdahl 2000); while we may have a feeling for which half 'contains' the function, we are far less certain of its location than in the case of speech. This could reflect a continuous distribution in a network, with varying 'means' and 'variances' of distribution.

'Distal' functional asymmetries

Finally we come to the area of asymmetry in which handedness resides, the functional asymmetries. Indeed, at this stage we can reflect that the prevalence of asymmetrical actions observed from single-celled creatures up (as mentioned above) must give pause to the blithe acceptance of symmetry of action as the norm. Functional limb symmetry perhaps starts to look a bit odd, even when the structural symmetry is so clear.

The argument that structural symmetry provides a fitness advantage in a world in which predators may come from either side may seem too simple. However, functional asymmetries can, by dint of practice and/or environment (Collins 1975) change during the lifetime of a creature. We can therefore compare two situations; in one, survival requires learning a new type of skill/shifting side preference, in the other survival requires growing two new limbs with the asymmetries reversed. Which is easier? With functional asymmetries we have potential performance benefits that can be modified within the lifetime of an individual. In an environment in which predators may come from either side, functional asymmetry combined with structural symmetry seems to have the edge.

Most structurally-bilateral species demonstrate functional asymmetries. Individual mice show a paw-preference actions (Collins 1969), parrots show clear claw-preference for manipulating food (Rogers 1980), and primates show clear paw-preferences for specific tasks (Steklis & Marchant 1987).

However, it does not appear that in any instances, for any of these tasks, can one demonstrate lateralization at a species level, that is, a consistent preference in the population under study. The exception appears at present to be the parrot, with only about 12% using their right claw to manipulate food (Rogers 1980). In terms of understanding the origins of human handedness the findings in primates could provide a better model, but overall a species hand preference bias has not been demonstrated (see review McGrew & Marchant 1997).

In humans, the measurement of 'handedness' depends largely on definition, and forms the focus of the next chapter. The measures are either categorical measures of preference, frequently expressed as a 'total score' of many 2 or more-category measures, or a probabilistic continuum of likelihood of use of one of two sides, or bivariate continuous measures of performance.

WHY LATERALIZE?

- Why not keep things equal?

Advantages of dominance

- Choosing a preferred hand

A potential difficulty when considering this might be distinguishing advantages that result from hand preference (from observed superiority in performance in a manual task, say), and hand preference that is a consequence of lateralized processing further 'upstream'. Hand preference may result from selection for function superficially unrelated to hand task performance, and therefore light will not be shed on why a hand is preferred by examining the hand's structure or function.

However, whatever the origin of the hand preference, the question remains; is there any measurable advantage in preferring a given side?
It then follows to ask whether
a) advantages accrue to use of a particular side, or just to focussing on *a* side, and
b) are these advantages related linearly, say, to the extent to which the preference is expressed?

Exploration of these questions in the specific context of human hand skill will be examined in chapter 2. In primates there are measurable advantages in the performance of primates using one hand over those that use two, or alternate, hands (McGrew & Marchant 1997).

It can be argued that, in terms of survival, having two equi-potent hands, enabling one to ward off attack from either side would be an advantage. In contemporary terms, having a gun in each hand is surely safer than just having one.

The use by infantry of a single rifle can be seen as a necessity resulting from a need to steady and aim the weapon, a limit imposed by technology. However, the singular lack of success of multi-turreted tanks could suggest that the limiting factor is not engineering (see Appendix B); a brain that appears to have two equi-potent halves, residing in a single organism, is maximising survival though focussing attention on single actions. Given our structural bilaterality, this will lead to our attention often being focussed on one side or the other.

The other side of this coin is the view that lateralizing a function actually allows for adaptive attentional splitting, ie. that if a task is specialised to one side, another task may be performed on the other side simultaneously. For example, there is evidence that highly-lateralized chicks detect a threatening target with shorter latency than nonlateralized chicks (Rogers 2000), suggesting the lateralized chicks can better feed (right eye, left hemisphere) AND be vigilant for predators (left eye, right hemisphere).

Finally, many 'sided' tasks are actually bimanual, with one hand taking a less conscious but nonetheless essential role eg. steadying the paper being written on, or holding the jar being opened. 'Dominance' can therefore be an observation about the side on which attention is focussed, an assessment of the subjective experience of the action, rather than an objective description of the action as a whole.

Disadvantages of dominance

- Disadvantages of preferring a hand

If an organism is bilateral, it can be argued that preferring one side for a given task is a handicap. Predators or prey might come from either side, and woe betide the individual if this is their weaker side. One could raise a similar point about having a specific cognitive focus of any sort.

It would seem, however, that it is better to have superior function which one can (by moving) bring to bear on a task, than inferior function represented bilaterally. It would seem that it is better to do one thing well, then another, than do two things simultaneously but less well.

One could also wonder about the disadvantages at having one hand functionally 'redundant'. However, this presupposes that lateralized actions are genuinely unimanual, whereas most 'dominant' activities can be reformulated as bimanual, whole-organism activities. The notion of 'dominance' arises from the focus of attention, and does not mean that only one thing is happening. Effective use of one hand not only depends on posture and head position, but often 'balancing' activities with the other hand eg. steadying the paper, holding a jar. It is noticeably harder to write on paper or open a jar (held in a vice) if one's other hand is immobilised or being held clear. Lateralization of function can be seen as a misinterpretation of what is in fact a balance between two active, sometimes opposing forces from each side.

Advantages of localisation of function

- chairman vs committee

The continuous measures (or potentially continuous measures) suggest another parameter to variability than mere sign or magnitude of a 'mean' centre of activity, that of variance. Another way of expressing this would be to say that some functions may be lateralized (or not) but are highly-localised, whereas others are more widely-distributed across the brain/cortex. The ultimate localisation of function in biological systems occurs at a cellular level, but while cells are capable of very complex responses to different stimuli, more complex functions demand more than one cell, so the issue soon arises how they should be arranged with respect to one another.

The brain can be seen as a large network of interconnected neurons. Such a model encourages comparison with 'neural networks', although attempts at such comparisons should proceed with caution (for a review of the findings and issues raised by neural network simulations of brain function, see Park & Young 1994).

Even with this model of brain organisation, however, there are tracts and commissures, bundles of nerve fibres that connect various parts of the brain together. These arrangements might just reflect local solutions to wiring problems, but there is one bundle of fibres, the corpus callosum, whose existence and path is dictated by anatomy; it connects the two hemispheres. Propagation delays across this are significantly greater than those within a hemisphere, so any process that is time-critical might avoid using this connection if possible.

The construction of expressive language is an example of a time-critical process. Aspects of language function do appear to be located in one hemisphere or the other. The existence of individuals with speech located on the right side of the brain suggests it is localisation to a side (rather than localisation to one particular side) that is required.

The analogy with neural networks is tempting, given that it offers the possibility of experimenting with network function in ways that would be impossible in a living creature. For example, one can alter the characteristics of the network and observe performance. The degree to which processes are localised can be altered by changing the degree of interconnectivity in a network, a change which can be considered akin to the process of synaptic pruning that occurs in the human brain into late adolescence (Huttenlocher 1990). It is found that as interconnectivity goes down (ie. processes are increasingly localised rather than distributed across the entire network) performance increases, up to a point (Hoffman 1997).

(It was then felt that further localisation led to the generation of outputs in the absence of any input, which was interpreted as the network 'hallucinating'. This can serve to caution the reader about the difficulties and biases that colour the interpretation of neural network behaviour).

It is perhaps not too prosaic to also draw an analogy with the performance of groups of individuals; an individual may get stuck on a problem, Hackney Borough Council might spend hours arguing, whereas a small working group may just get on with the job in hand.

Disadvantage of localisation of function

A clear advantage of a distributed network is resistance of function to physical damage, but a small area of localised function could be 'wiped out' by a small local problem eg. bleed, clot etc. While there is clear evidence that function can be recovered following such an insult, or even 'taken over' by other areas in time, a widely-distributed function would be more resilient still.

Similar thinking led in the 1960's to the development of a computer network by the Advanced Research Projects Agency (ARPA), itself formed as part of the US government's response to the then Soviet Union's launching of Sputnik in 1957. 'ARPANet' was a network of computer communication nodes that could maintain function in the event of a nuclear strike, by not having any one node acting as a central, vulnerable, 'hub'. This network is now seen as the forerunner of the Internet, and the latter demonstrates a great deal of resistance to local failures. While the individual components remain vulnerable, the 'network' as a whole survives. The same view may be taken of the consequences of brain injury.

However, the brain is contained in a fairly solid bone box, and the incidence of localised insults is low throughout the reproductive years, so any selective drive away from localisation has an uphill struggle against the more immediate and wide-reaching advantages of maximised function.

Discussion

The perception of symmetry and asymmetry stem primarily from an exercise in data reduction. Thus our perceptions of objects as symmetrical feels intuitively straightforward, but this perception is not necessarily correct. The Mirror Paradox, that objects seen in a mirror seem reversed left-right but not up-down (see appendix C) should serve as a cautionary tale. Interpretation of data on sidedness can be very instinctive, and very wrong. Easy acceptance of an object's 'bilateral symmetry' may result from our own external structural symmetry.

'Laterality' is a statement about a thing in terms of deviations from a specific hypothesised state of symmetry. Thus any measure of laterality may not generalise beyond its original context. Consistent population 'laterality' measured from one perspective, may simply be a consistent absence of asymmetry, measured from another. It is necessary to be as clear as possible about what the initial state of symmetry is, and why this is the best formulation for the given situation.

Lateralization in biological organisms is the rule, not the exception. Vertebrates have a bilateral structure or an asymmetrical structure, depending on your viewpoint; asymmetry sets in too early to satisfactorily distinguish which is 'primary'. Concepts such as 'linked asymmetries' remind us that a functional 'explanation' of the origins of a given asymmetry may be fallacious and unnecessary, and 'fluctuating asymmetries' can account for any asymmetry distributed 50:50 in a population without needing any fitness advantage/genetic basis. Asymmetries distributed 50:50 in the population do not need a 'reason' to have developed at all.

Finally, it is clear that having speech production localised to the left hemisphere is not exclusively human. Similarly, the ability of an individual to prefer their right hand for a given task is not exclusively human. However, the right hand preference for writing in human populations does appear to be unique, far greater than the greatest functional population asymmetry in primates. The right-bias in humans appears more a step-function distinguishing us from the other great apes, than a point on a continuum.

What is of interest, therefore, is the means by which the right-bias in the human population is achieved, as this seems to be a specific marker of the human species. Handedness as a variable offers the possibility of explaining variance between man and his nearest relative. Whether merely associated, or actually linked with other 'species-defining characteristics' of mankind such as generative language (Corballis 1991), pursuing the origins of population handedness bias is worthwhile, as it may have explanatory power in determining the true origins of human uniqueness.

Chapter summary

A vast array of objects in our physical environment are seen to display symmetry. This is primarily a consequence of visual analysis and data reduction; no causation is implied. Even such observations about ourselves are no more than skin deep.

'Laterality' can mean any conceptualisation of a deviation from symmetry; it can mean almost anything. The universe is asymmetrical on many levels, and this asymmetry can be conceptualised in many ways, although all may then be termed 'laterality'. Biological organisms can be asymmetrical on an individual level without this being under genetic control, but on the whole do not demonstrate population biases in functional asymmetries.

The human form, as with most animals, appears structurally symmetrical but functionally asymmetrical. The human population hand preference bias of 9:1 R:L seems exceptional, and is perhaps a feature that defines the species.

Chapter 2: Measuring handedness

"HANDEDNESS" AND "LATERALIZATION"

Introduction

- Why measure handedness?

In experimental sciences, measures have a tendency to degenerate from what you want to measure into what you can measure. Pragmatism is often necessary in order to ensure measures are reliable. However, subtle changes in validity can occur as measures are 'developed', such that a highly-subjective, interesting measure can be replaced with a highly-objective but wholly uninteresting variable. Measuring handedness seems especially vulnerable to this critique, especially if one assumes one is actually interested in lateralization in the brain, not the hands.

Lateralization of brain structure and function is readily perceived as 'more fundamental' than lateralization of peripheral functions. The suggested nomenclature of proximal and distal functional asymmetries reinforces this hierarchy. However, it also highlights the absence of distal structural asymmetries, in stark contrast to the numerous proximal (cerebral) structural asymmetries, many of which are seen in other species too. That handedness correlates with structural brain asymmetries is clear (Galaburda et al 1978), but in our current state of knowledge this imperfect correlation is difficult to do much with. There is some recent work looking at associations between hand skill lateralization and verbal activation on fMRI (Loring et al 2000), although the numbers of cases are necessarily small. Further, in a review of the relationships between functional and structural brain measures, Beaton noted that "Neuroanatomical asymmetries may relate more to handedness than to language lateralization" (Beaton 1997).

The observation that makes the hand preference population bias so interesting is that the distribution of hand preference for writing in human populations is 9:1 R:L. It has been so since the dawn of homo sapiens, independent of geographical location, and this despite the fact that each hand is the anatomical mirror-image of the other. Other species show population biases for hand-preference; the controversial claim is made by some authors that there may be a population right-preference for paw use in some species of monkey of up to 60% (McGrew & Marchant 1997). Nevertheless, this is a long way off the finding in human populations.

Further, although there are a vast number of structural and functional asymmetries one could measure, the correlation between them is highly variable. Our understanding of how they are associated may advance to the point where we can measure and talk of an individual's overall 'lateralization profile' (Bryden et al 1997), but this remains in the future.

Lacking a hypothesis about the origin of these biases, we are left with this remarkable discontinuity. Historically, the first to come were observations of hand preference, referred to in many ancient texts. This was long before the brain was recognised as the point of conscious origin (instead of the heart, say), and of course longer still before understanding of the bilateral nature of the brain informed understanding of hands being wired to opposite hemispheres. The historical record, both written and implied (eg. from the orientation of flint-chippings) suggest the right-bias in the human population intriguingly pre-dates written language by tens of thousands of years (Coren & Porac 1977, Spenneman 1984). Thus handedness is interesting, and may be telling us something of fundamental significance if we wish to understand what makes us human.

- Why take two measures by side, rather than measuring 'lateralization' directly?

However, handedness is such a specific example of lateralization. Why can't we examine some continuous measure of lateralization? Unfortunately there is no external measurable 'centre of gravity' that deviates in an individual either side of a midline like a meter needle, to indicate an individual's 'lateralization' on any measure; we are externally bilaterally-symmetrical.

The only exception could be assessment of deviation of an essentially 'midline' structure. However, the only examples known to this author (deviations of the nasal septum as measured by maxillofacial surgeons, the 'John Thomas sign' (Thomas, Lyons & Walker 1998), whereby the penis is said to point to the side of a fractured hip, and a qualitative measure of "deviations of the nose with respect to the chin and forehead" when examining for ‘minor physical anomalies’ (Lane 1997)) are difficult to consider as correlates of cerebral structure or function.

We shall therefore review the commonest measure of functional lateralization in man, measures of handedness:
- the types of data: performance and preference, and how these are gathered
- the laterality index
- potential problems with the concepts, data gathering, and analysis, bringing us back to asking the question
- "What is the hypothesis?" ie. what do we think handedness is, and how the answer to this question shapes further inquiry.

TYPES OF HANDEDNESS MEASURE

Preference measures:

Some measure is taken of which side would be preferred for a given task. Such measures can be obtained by
- Observed preference: observing which hand is used for a particular task
- Recalled preference: the subject is asked which hand would be used.

- Many meanings, many constructs

Preference is a word like laterality, that can mean any number of things. Further, variability will be present in any such measure (Raczkowski 1974), and this encourages a notion of 'consistency' as a meaningful variable, ie. consistency with which a given hand is used for a given task. Higher consistency indicates a greater degree of preference, decreasing to 50:50 use of either hand ie. no preference overall (although an apparent bias if the action is only observed once). Environmental biases can influence preference, so one could have numerous other notions of preference, for example the hand used when a task was essential or urgent. The latter could then be considered to be 'more significant' than day-to-day preference in terms of 'fitness'.

- Not a consistent trait?

The physical environment can also affect which hand is preferred for the task (Collins 1975). For example, it is unlikely that any task is 'only ever' performed by one hand. There will probably be some environmental manipulation that can force use of the other hand, even if that involves tying one hand behind your back. What is striking is that hand preference for writing displays a great deal of robustness and consistency, compared to a number of other tasks.

- Assumptions of homogeneity best avoided

Variability between occasions can make results difficult to interpret. If a person uses one hand on one occasion, and another on another, what does this mean? Clearly, one needs many trials under similar conditions in order to accurately 'quantify' this inconsistency.

(In the 1974 Raczkowski paper looking at the ‘reliability’ of hand preference, associations between stated and observed hand preference, and recalled preferences, were compared with actual hand used on one occasion, as well as a repeated recall of preference. Agreement between the two recalls, and the recall and the observed preference varied in all measures (apart from 'hand used to draw the top card from a deck'). However, the study failed to measure 'consistency' as a quality of individuals; given only two responses, the chance of consistency given just two observations was high anyway. Assumptions had to be made about the homogeneity of the sample in order to equate uncertainty in the population with uncertainty in individuals, and thus interpret the results).

Thus, the association between reported & observed hand preference remains unclear, although the reliability of reporting of preferred hand for writing is very good.

Performance and size measures

Performance measures in handedness & lateralization research are invariably two continuous measures taken of

- size of a 'symmetrical' region on either side
- performance on a task, such as time taken to complete the task, a quantitative measure of precision at a task, or the rate at which the task can be repeated
- performance at a task when initiated from one side or the other.

Measurement schedules

Single subject

- Single measure

Suitable for a within-subject hypothesis, requires well-established test-retest reliability

- Single measure repeated

If measures are repeated in one individual, one can demonstrate the effects of test-retest reliability, practice, learning and fatigue, depending on their relative magnitude,

eg. dichotic listening tests can remain ambiguous even after many repeats, with apparent speech dominance changing sides between tests because of the high level of noise / low reliability of a single test.
- Multiple measures
Multiple 'related' measures in individual may look better, but interpretation of this is problematic in the absence of a hypothesis; if measured performance is highly correlated between tasks, one might be effectively just repeating the task, thus confounding through 'bloated specifics' and practice. On the other hand, if measured performance between tasks is uncorrelated, one might legitimately wonder exactly what it is that is being measured, if one is attempting to investigate a 'basic', underlying laterality.

Many subjects
- Single measure
A single measure in many individuals will demonstrate how ability is distributed in the population. There are numerous potential confounding factors eg. prior exposure to learning, so sources of sampling bias and the possible effects of the confound would need careful consideration.
- Single measure repeated
Allows one to quantify the effects in individuals described above, and then perhaps remove them from the model eg. remove different rates of learning and fatigue, and just leave group effects.
- Multiple measures
Multiple single measures in different areas will enable one to explore correlations between the measures and analysis of 'noise', and by group effects, although it will not tell you which measures are more significant unless a hypothesis is being tested.

Important confounding factors: learning, fatigue and maturation
- Learning
Repeated performance on most tasks will improve; this is one definition of practice (Concise Oxford Dictionary 1999: "a repeated exercise in an activity requiring the development of skill."). The issues here may be:
"Do both hands learn equally fast, or is there 'differential learning' by hand?"
"Is there 'crossover learning', such that practice with one hand improves the next attempt by the other hand?"
This latter effect would make testing vulnerable to bias by hand that first attempted the test, especially if there is a differential effect by hand here too.
- Fatigue
Contrariwise, repeated testing may rapidly fatigue a subject both physically and mentally, leading to a fall-off in performance. Again, given sufficient advantage in one hand, this hand may physically tire first, leading to a decrease in the hand performance difference over time, or even a reversal.
- Changes with maturity
Absolute performance, as well as the considerations above, may be associated with age, due to experience in allied tasks, or greater 'neurological maturity' (see chapter 3).

Tests in practice

A vast array of measures of laterality have been developed over the years, for the most part representing aspirations to reliability and ease of administration rather than ethological verity. The tests may be internally consistent, but whether and how they apply to tasks that people perform in their everyday lives is unclear.

Preference questionnaires

All preference questionnaires:
- propose an action
- ask which hand is preferred for this
- categorise as - R or L
    - R, Either, L
    - R, mostly R, Either, mostly L, L

They are developed by piloting a large number of questions, then using data-reduction techniques (eg. factor analysis) to minimise the shared variance ie. remove actions whose preference is so highly-correlated with preference for another task on the questionnaire, that no further information on variability is added by their inclusion.

For adults, such tools can be administered as a questionnaire. For children who are too young for this, the questions can be posed and the action mimed. In the case of the Annett questionnaire, it is advised that the option 'Either' is not specifically offered, presumably as this leads to a higher level of this response.

In adults, then, these are often recalled preferences, whereas in children it can be seen as recalled and 'signed' by miming, or actually enacted. The responses are reliable, and they are certainly valid measures of verbally-expressed preference.

Performance measures

Performance at a given task can of course mean many things. It can mean the time taken to do the task, at all, for the first time, the average time taken to do it many time, the precision with which a task is performed,

Types of Tests

Tests of performance are usually considered in terms of a type of action being tested, whether purely descriptive eg. 'a match-moving task' as opposed to 'a box-ticking task', or a more sophisticated grouping such as 'finger dexterity' as opposed to 'manual dexterity'. The latter groupings can be paradigmatic eg. 'aiming' vs. 'reaction time' tests, or can arise post-hoc out of data-reduction techniques eg. 'fine dexterity' vs. 'manual dexterity'.

The wealth of tests suggests strongly that measurement is not the problem, rather that there is little clear idea of which are important measures and which not.

Size e.g.:
- Planum temporale, length of sylvian fissure etc.

Tests of speed e.g.:
- Purdue pegboard (Gardner & Broman 1979), Annett Pegboard (Annett)
- Marking dots in a line of circles (Tapley & Bryden 1985, originally described by Stott, Moyes & Henderson 1972), or boxes (NCDS)
- Finger-tapping & finger-opposition - speed at which fingers can be tapped against a surface, or opposed (Denckla 1973)
- Arm pronation & supination, heel-toe movements - speed of repetition of large-scale movements (Denckla 1974)
- Match-picking - time taken to move 20 matches from one box to another (BCS70).

Tests of accuracy e.g.:
- Line drawing tasks, where the precision with which a straight line is drawn between two reference lines is measured
- An extension of a speed task eg. marking boxes with crosses, then counting the percentage of Xs that extend beyond the box (see Barnsley & Rabinovitch 1970)
- Square-tracing task (Bishop 1980a (book) - number of deviations beyond the guidelines. Used in investigation of pathological left-handedness.

Others - aiming, reaction time, arm movement etc. (Barnsley & Rabinovitch 1970)

These tests of performance show satisfactory reliability, but do not correlate well with each other. Analysis of preferences can be seen to generate a single 'handedness factor' (Bryden 1977, Williams 1986), three factors (Loo 1979), or four factors (Liederman and Healey 1986). Indeed, the more tests that are employed, the more 'underlying factors' there appear to be; an examination of 32 tests (Barnsley & Rabinovitch 1970) generated no fewer than nine underlying factors. More recent work continues to refute the notion of a single 'underlying' factor of laterality (see Boles 1998a & b for a review). Further, tasks that prospectively seem very similar - eg. fine manipulation of little bits of wood - can have very different distributions indeed, as we shall see later comparing a box-marking task with a match-moving task.

Any task will employ many neurological systems working in concert, and discovering that there are many of these, each with an independently- ‘sided’ contribution, is perhaps no surprise. In the absence of a reason to see one or other measure as ‘fundamental’, it is difficult to do more than marvel at the complexity of it all.

- Hybrid measures

There are also hybrid measures that combine features of performance and preference. An example of this is the Quanitification of Hand Preference Tasks (QHP; see Bishop 1996, Calvert & Bishop 1998). An extension of the 'long pegboard' measure (Bryden et al 1994) individuals perform a number of tasks involving reaching for, pointing at and placing objects. In each case the hand used for the task is recorded (binary categorical preference), as a function of the displacement of the action from the individual's midline (continuous measure). This method is said to discriminate degrees of righthandedness better than other measures, while avoiding the reliance on seeing some particular, single task as THE measure of handed skill.

THE LATERALITY INDEX

Presentation of data

The commonest approach is to summarise results in a 'laterality index' or 'laterality quotient'.

Preference measures

A laterality index derived from preference measures is a summary of the distribution of expressed preferences. Individuals are asked the hand they prefer to use to perform a given task, in a list of different tasks. In some questionnaires, extra weighting is given the more strongly a preference is expressed. Items are then individually-scored, eg. 'Left' = 0, 'Either'=1. 'Right'=2. The laterality index is a (in some cases weighted) sum of these scores.

Performance measures

These consist of a measurement of size of a (bilaterally-represented) structure, or performance at a unimanual task, on each side. Commonly a ‘laterality index’ is then calculated as an expression of the difference between the sides.

There a several ways of expressing this difference:

- The difference (R-L).
The advantage with this measure is that units are easily interpreted. The chief disadvantage is that small relative differences between sides in a high-scorer can generate a larger index than similar-magnitude differences in a low-scorer. Examples of such a measure may be found in the work of Marian Annett (Annett & Manning 1990).

- Relative difference (R-L)/(R+L).
This is the absolute difference divided by total performance. It may be felt that simple differences between the sides are being confounded by absolute performance. 'Standardising' by overall performance results in relatively large differences in poor performers not being drowned-out by small differences in good performers. (McManus 1985)

- Ratio (R/L)
Not popular, presumably because of its neurosis in a field where R or L preference or performance can drop to zero!

Interpretation of results

Laterality indices are then taken to describe a 'degree of laterality'. However, laterality coefficients can become Humpty Dumpty's 'glory' (see Chapter 1) writ large. Consider a laterality coefficient running from -1 (entirely left) through zero to +1 (entirely right). A score of 0.1 +/- 0.05 could be seen as clear evidence that the individual is
- R-handed,
- equi-handed, or even
- relatively left-handed

The interpretation depends on your hypothesis of what constitutes handedness in this instance.

Similarly, if in a given population 90% of subjects have an index of about 0.1 and 10% have an index of about -0.1, is this
- a R:L preference ratio of 9:1,
- a skewed measurement from a biased 'instrument', or
- a population in equipoise?

This is tricky; 'absolute' equipoise is terribly unlikely given measurement error. The interpretation depends on what you believe about the significance of a small value of this particular laterality index.

It should be clear by now a laterality index generated from sided data does not necessarily 'mean' anything in the absence of a hypothesis about its origins. Further, generating a laterality index makes assumptions about the situation, immediate, almost hidden assumptions, that mean the index may not generalise, or may not be a true measure at all.

DISCUSSION

Reliability & validity - practical

Preference measures

- Internal consistency, but questionable validity

Most of these 'handedness inventories' have been validated to an extent. Individual items have internal consistency within individuals, and over time (eg. Steenhuis 1990). Some attempt is often made to weight individual items to adjust for their relative 'contribution' to the handedness index, and measures of internal consistency have been used to minimise the number of items (Curt et al 1997). However, in the absence of any neuroanatomical understanding of the functional relationship between the tasks, the items are essentially arbitrary.

- Skilled vs unskilled tasks

Two main factors, for 'skilled' and 'unskilled' activities, emerge from factor analysis of preference scales. While this would seem to support the notion of a general hand preference for skilled tasks, and another for unskilled tasks, one has to be wary of accepting such conclusions (Steenhuis & Bryden 1989, Obrzut et al 1992, Singh & Bryden 1994) at face value:

- while 50% of the variance is accounted for in the 'skilled task ' factor, variance accounted for by the 'unskilled factor' is about one tenth of this ie. much noisier.
- 'put nut on a bolt' is seen as 'unskilled', 'picking up a comb' as 'skilled'; which task, in practice, requires more skill?
An alternative interpretation is that there is one strong, convincing factor, weighting heavily on writing hand.

- Recall confounded by writing hand?
Worse still, they are frequently recalled items, rather than direct measures. Not only can recalled preferences differ from those directly measured in the same subjects(eg. Bourassa, McManus & Bryden 1996), recall could also be a source of confounding. Martin & Jones recently found that recall of widely-available 'sided' information was heavily-confounded by writing hand preference. They discovered that recall of the direction the Queen's head faces on a stamp, the orientation of a recent comet's tail (visible for several weeks all over the world), and a digging workman on a road sign, were all affected by handedness; an individual's hand preference makes them more likely to correctly recall objects orientated in the opposite direction. For example, right-handed individuals are more likely than left to correctly recall objects as left-facing, and left-handed individuals more likely to correctly recall objects as facing right (Martin & Jones 1998, 1999).

This work, suggesting that recall of sided events or objects are mediated via motor imagery, has profound implications for any work based on recalled preference measures. Recall of parent's handedness is affected by subject's handedness (Kang & Harris 1996). It would seem very likely that recall of sided actions may be confounded in a similar way. This could also account for apparent correlations between task preferences on a questionnaire (eg. Liederman & Healey 1986). Recalled and actual preferences in other modalities have been examined and found consistent (Coren & Porac 1978), but such confirmation, especially in an ethologically-valid setting (see below) has not been done for the finer gradations of preference present in most questionnaires.

- Ethological validity of primate observations
The nature and setting of many handedness tests are themselves sources of uncertainty about their findings. In a stinging review, McGrew & Marchant point out that the ethological validity of a test of preference is <u>all</u>, given the adjustment of any functional response to its environment. This point is illustrated by Collins' earlier observations in mice that their paw preference is determined to a large degree by the 'handedness' of their environment. Interestingly, the adjustment possible through environmental manipulation was only from 50:50 to 90:10 - there was a limit to how much a chiral environment can influence the preference. McGrew & Marchant also point out that observations of side preference for a task have often been made with numbers too small to take account of the uncertainty in the data, concluding that we presently do <u>not</u> have evidence of substantial population preference in non-human primates.

- Ethological validity of laboratory tests
Naturalistic observational studies of hand preference for tasks in humans, similar to those conducted on primates, would be time-consuming and methodologically

challenging, although not beyond current technology (eg. 'Big Brother', Channel 4 2000). There is a need to see how big an effect this 'chiral cognition' has on handedness questionnaires, given the huge proportion of handedness data they represent.

Data on children, where they mime the response, can be uncertain, given the artificial nature of the surroundings and lack of any mechanical feedback should they use the 'wrong' hand eg. using scissors with the wrong hand rapidly reminds one this is the case, combing ones hair with the wrong hand can lead to attempts to comb 'across the grain', again not obvious if one is miming.

Overall, then, despite their seemingly straightforward nature, preference measures as recalled are questionable on a number of grounds:
- the extent to which they are confounded by preferred hand
- the validity of the practice of summing scores on different tests
- the validity of the mixture of activities asked about
- the face validity of examining tasks not obviously distributed in the population 9:1 R:L at all. They may reflect fluctuating asymmetry, but it could be argued that what are of interest are the factors leading to the 9:1 population bias. If they don't show this, or the data suggesting they do is confounded by preferred hand for writing, why measure them at all?
- questions over the ethology of current 'tests' of preference, especially in primate work.

Performance measures

- Confounding effects of learning?
Bishop dismisses out of hand any test involving holding a pen. 'Differential performance in the two hands is likely to be strongly influenced by practice in writing' (Bishop 1990 p.178). This assertion deserves close examination.

We may suppose that the differences between performance by sides may be a consequence of:
1. Fluctuating asymmetry - noise
2. Some underlying preference to use one side or the other, distributed unevenly in the population, and
3. Practice differences that may be an inevitable consequence of 2.

If the sided 'bias' dictates preference alone, the differential effect of practice will separate out the populations into two peaks, as is seen in ticking, which does use a pen, and tapping, which doesn't. If it also contributes to the absolute difference, the separation might be greater still.

The prediction should be that the separation is bigger in a practised task than un-practised. It is therefore interesting that <u>absolute</u> speed of finger-tapping is the same whether you're a pianist, a typist, or not in a 'tapping profession' at all. As is the R-L difference. Practice might not seem be responsible for the bimodal-distribution (McManus 1986) seen in finger-tapping measures, at least.

Data gathered in young children has been interpreted as supporting the notion that hand skill is initially unimodal (age less than 3½yrs), and that two distributions by preferred hand separate out as the children grow older (Curt et al 1992). However, this conclusion could well be a type 2 error: the 7 lefthanders in the relatively small sample of 43 children under 3½ still have laterality indices clearly skewed to the left even in this young age group.

Related work suggests that the performance difference (ie. R-L difference) increases a little in practised tasks, although observed preference is fixed by the age of three (McManus et al 1988), and degree of preference (ie. expressed certainty of preference) increases a lot (Dellatolas et al 1997) between ages 3 and 9.

In apparent conflict with these findings is earlier work finding the degree of performance difference *decreases* with age (Denckla 1973, 1974). However, perusal of the data in the 1974 paper demonstrates that this observation is based on conceptualising the difference as an actual difference (R-L); if one calculates the difference as a relative difference ((R-L)/(R+L)), the change over time is equivocal, or even (again) a small increase in difference.

In the 'un-practised' peg-moving task, the effects of practise show within a few trials. Significant linear effects (and possible non-linear ones too) are seen in both hands on absolute performance and RL performance difference (Tan 1990). This will affect any 'laterality index', and suggests there may be systematic error introduced in test populations by repeat testing, or failing to separate 'unpractised' and 'more practised' groups. One could therefore argue that ethologically highly-practised tasks, in which any 'learning' has already been saturated, could be more stable under testing than un-practised ones. Further, a high degree of learning in the general population suggests the task is more likely to contribute to selection pressures than another task which is not often encountered in normal life.

In the context of the analyses to come later, the fact is that data is only available on two tests, each performed once. Any effects of practice will be there, or not, depending upon subject's prior exposure to this. There are no independent measures of practice. Moreover the relationship between practice and function might be too central to notions of how brain function develops, to dismiss as mere confounding anyway, as will be discussed at the end of this thesis.

- Preference a function of Performance?

Dorothy Bishop (1989) found an elegant way to transform a normally-distributed performance curve into the characteristic J-shaped preference distribution seen for most preference questionnaires, simply by assuming that preference was a threshold function of degree of R/L difference.

While this is reassuring, most data can be accounted for by ad-hoc adjustment of the thresholds involved. Again, without a testable theory about the origins of hand preference, we proceed no further. Causality could work either way; it seems 'obvious' that one will prefer to use the more able hand, yet there are plenty of individuals who prefer to use their 'weaker' hand.

- Performance a function of Preference revisited
Of note is the finding by McManus (1992) that autistic children show 50:50 skill distribution while retaining a 9:1 RL preference, suggesting preference is 'more fundamental' than skill. The possible 'independence' of preference & skill is also intriguing. On the other hand, it is not clear whether they simply do not gain benefit from practice, or whether they are not practicing as much. One could also argue about the particular performance test being appropriate or sensitive-enough to pick up a difference in this special group.

Further, this may represent a false dichotomy. Categorical preference-style differences proximally can result in a continuous one distally, and vice-versa, by the process of linked and fluctuating asymmetries. From the perspective of structural equation modelling, any distribution you can model using N continuous unseen 'factors' can just as satisfactorily be modelled with N+1 categorical unseen factors. The data will not tell us which it is (simply widening one's concept of handedness to 'a handedness preference score' leads to the conclusion that handicapped groups are more symmetrical than normal controls in preference too (Mandal et al 1998)).

Overall, the orientation of internal structures are R or L (arrangement of heart vessels, situs etc.). Where there are two bilaterally-represented regions, or functions, we can generate an index of difference. These two situations may suggest a difference in the point during development when asymmetry set in. However, it may just remind us that there are potentially important qualitative as well as quantitative differences between the types of observation being made.

For the time being, we are left with the measures.

Reliability & validity - mathematical

While debate has raged over which measure of handedness is 'best', there have also been numerous concerns over mathematical aspects of laterality indices and the manner in which they are analysed.

- The standardised index makes more assumptions about the data than simple difference. It assumes that processes interfere with performance as a linear function of performance, which may well not be true eg. a small increase in subjective difficulty may cause a greater drop-off in performance in a handicapped individual than in a normal.

- Richardson (1974) has commented already that a 'theory independent' measure of laterality, while desirable, may most safely exist as an ordinal, rather than a numerical measure.

- Pursuing the 'theory-independent measure' idea, Marshall (1975) has observed that laterality measures can be 'confounded' by differences in subject's accuracy / performance. For example, children at 10 are less lateralized (R-L) than at 5, as test performance at 5 is less (R+L). The paper observes that while researchers are keen to determine whether such and such a task is more lateralized than another (and then to posit theories based on such findings), they are almost uninterested in what they mean by 'lateralization', assuming it to be a known property in each subject. Similarly, Bryden & Sprott (1981, 1983) have pointed out that laterality indices as currently derived depend on absolute performance, and proposed the use of the log odds ratio instead. Few researchers have taken up this challenge.

- McManus (1983) explored the fact that when comparing the means of two groups, each drawn from a mixture of sub-groups, if group membership is not randomly-distributed then linear models (eg. t-tests, ANOVA) are not interpretable, as the variance of the two groups will be different. A maximum-likelihood method is presented that avoids this problem. This potentially strangles factor analysis of lateralization indices at birth. While numerous authors have compared indices on tests, using factor analysis to search for an underlying 'lateralization factor', McManus' critique would suggest these efforts are methodologically invalid, as a given value of index in one handedness group is not 'equivalent' to the same value in another (as a proportion of the variance of that group). This difficulty also applies to data from hand preference questionnaires (Peters & Murphy 1993).

- Bullmore (1995) found a correlation between height of his subjects and the standardised right-left difference in sizes of regions of interest in MRI scan data, and attributed this to the fact that the contribution to each side is not a linear function of height. Put simply, dividing by (R+L) to 'standardise' the difference presupposes that the contribution to the difference is symmetrical ie. that R&L each vary in a similar fashion, which they do not.

Thus, statistically as well as conceptually, the benign and seemingly intuitive laterality indices are in the dock.

WHAT IS THE HYPOTHESIS?

There are two main concepts of 'underlying handedness'.

1. "Handedness is the primarily-determined binary category of preference"

- a varying degree of lateralization of underlying skill gives rise to a hand preference via a 'threshold' of advantage being exceeded. It may be a varying likelihood of being right-handed, or a varying likelihood of using the right hand at a given time. Thus a binary category of handedness can still end up on an apparently continuous scale of probability of use, or proportion of use, in a variety of tasks. The hand may be preferred between 100% and 0% of the time.

2. "Handedness is a binary categorical 'summing up' an underlying continuum of lateralization"
- although continous measures all consist of two continuous variables, of skill/performance by side. All measures of laterality of performance, activity or size, are bivariate.

Despite these concepts being different, and there being many more ways of gathering data on these two measures (see chapter 1), the results, such as population histograms from two very different experimental paradigms can look similarly-distributed. The temptation is to compare them directly, without consideration of the very different mechanisms that might bring about such distributions. Thus hypotheses can be supported or rejected without consideration of what type of lateralization is being examined, or whether two types are in any sense comparable at all. Hybrid measures such as the QHP, deriving from a mixture of concepts – categorical and continuous/threshold models - perhaps make interpretation of results more rather than less difficult.

Finally, what mustn't be lost sight of is that we are making these measures with an aim in mind. We are characterising handedness, and variations in handedness, in the hope that valid and reliable measures will ease understanding of its
- distribution in the population,
- relationships with other measures of function, and
- origins.

If we are pursuing an understanding of a species-specific quality, we must resist clouding our measure with other measures that while valid, reliable and well-distributed, may reflect mere confounding, or fluctuating asymmetries.

CONCLUSIONS

As Humpty-Dumpty might have put it: "There's laterality for you". It seems that we can pick and choose whatever measure or concept we want, and call it laterality.

Much of the critique is 'the perils of summary in the absence of hypothesis'. Refining measures methodologically in the absence of any real test (or theory) of external validity does little apart from introduce noise. The conceptualisation involved in creating any laterality index is also rather uncertain, lacking as it does an underpinning by any hypothesis for the origins of lateralization. There are also several statistical problems with laterality indices as popularly conceived.

However, we can return to where we started from, that hand preferred for writing IS handedness - it is more stable over time and cultures, between repeated measures, different observers, on recall and so forth, than any of the other measures. All other measures of functional lateralization are if anything less reliable, and of increasingly dubious face validity (see Raczkowski, Kalat & Nebes 1974). While decisions over hand choice in other tasks are interesting, in the absence of any theory of their origins they are potentially all just obscuring our essential ignorance. If we are interested in handedness performance measures, then, looking at performance at writing, or a task that associates strongly with this skill, does not seem too obscure.

This is not meant simply as an apology for using the handedness measures explored later in this thesis, although it undoubtedly is. Rather, it is a rationâle for not simply working to develop 'better and better' measures of handedness, but seek to understand and confirm the simple observation, specific to the preferred writing hand, that we already have.

Chapter summary

All sorts of things that look like handedness can be measured. Arguments that attempt to strip off hand preference from hand skill, or explain differences by learning effects, can easily become circular. Laterality indices come with a lot of conceptual and mathematical health warnings. Thus, while tempting to consider 'handedness' to be some general underlying construct of task proficiency by side, attempts to formulate this construct get lost in a wilderness of noise, confounding and poor correlation between measures.

Handedness perhaps remains the answer to the question "Which hand do you write with?".

Chapter 3: Lateralization and outcome

The associations between lateralization of brain function, cognitive function and psychosis are the context of this thesis.

Therefore we will next briefly examine
- associations between laterality and cognitive function
- attempts to explain the distribution of handedness as the result of environmental pressures
- recent genetic theories of handedness, and their predictions (if any) about associations between cognitive function and measures of lateralization
- associations between psychosis and cognitive function
- attempts to conceptualise and account for the distribution of schizophrenia
- associations between psychosis and laterality, and
- the Crow hypothesis, and its predictions of an association between cognitive function and measures of lateralization.

The chapter ends with a summing-up of the factors common to the two fields, and any predictions theories from either fields make about associations between lateralization, cognitive function, and psychiatric illness.

Theories of handedness

Any model of handedness must account for a large number of observations about its distribution and inheritance, some of the key amongst which are:

1. The distribution of handedness appears robust even in illiterate contemporary societies, throughout the human history, and varies little with geography (Bishop 1990 pp. 11-15, Corballis 1991 pp. 86-90).
2. Left-handedness runs in families, but only weakly, with almost half of left-handers having no known left-handed relatives (McManus 1995).
3. Two left-handed parents have left-handed children in only about 25% of cases (McManus & Bryden 1991)
4. Monozygotic (identical) twins often differ in their handedness, although discordance is slightly less than in dizygotic twins (McManus & Bryden 1991).

There is evidence that environmental factors can modulate the rate in the population; social pressures against writing with the left hand were stronger and rates of left-handedness lower at the beginning of the last century compared to today. However, left-handedness rates never get much over 12% even in the most liberal of cultures. The resilience of handedness rates in themselves strongly point to a biological rather than a social origin. Thus a biological model, with the above characteristics, is required.

- Social pressure and prejudice

Left-handers are in a minority, and as such are stigmatised. The American psychiatrist Blau saw left-handedness as a manifestation of 'infantile negativism' (Blau 1946), and Sir Cyril Burt, a British educational psychologist, wrote in 1946 "They squint, they stammer, they shuffle and shamble, they flounder about like seals out of water". Subjected to such a tirade, so might the reader. A reaction against the apparently universal prejudice against left-handedness was the view that its rarity was the result of these prejudices, without which it would be as common as right-handedness. As the novelist Charles Reade wrote in 1878 "Every child is even and either handed until some grown fool interferes with and mutilates it".

- Handedness and cognitive function

Such arguments clearly suggest functional disadvantages to left-handedness. However, systematic attempts to confirm such disadvantages have failed. Even large-scale studies, such as that conducted in the 1946 National Survey of Health and Development (NSHD) UK birth cohort by Douglas, Ross & Cooper (1967) failed to find any significant differences between handedness groups on several tests of mental ability and school attainment. These findings were essentially confirmed in a similar investigation of the 1958 National Child Development Study (NCDS) by Calnan and Richardson (1976); although they found significant differences between handedness groups, these differences were "slight" (amounting to about one-tenth of a standard deviation). More recently Curt et al (1995) again found no relationship between handedness and language development in a group of pre-school children. It seems clear that lefthanders are not disadvantaged with respect to right-handers.

Handedness considered as a continuum of preferences has also been examined with respect to cognitive function. Annett (1970) demonstrated a U-shaped relationship between vocabulary and hand preference in a randomly selected group of 219 children aged between 3½ and 15, with mixed-handers showing a disadvantage compared to right- and left-handers, of around half a standard deviation ($p<0.1$(sic)). However, several authors including Ullman (1977) and Richardson & Firlej (1979) have subsequently failed to confirm a consistent relationship between inconsistencies in lateralization and poor intellectual performance.

More recently handedness considered as a continuum of right- versus left-hand performance has also been examined with respect to cognitive function. Annett & Manning (1989) demonstrated in 313 primary schoolchildren that reading ability was poorer in individuals with either very small or very large differences between their hand skill on a peg-moving task. Whittington & Richards (1991) divided children in the 1958 NCDS cohort into "strong left-handers" and "strong right-handers" on the basis of their preferences and their hand skill at a box-marking test (of which more later), and found non-significant trends in the same direction. An error in the marking sheets used in the Annett & Manning paper was later detected, and when corrected the statistical significance of the original findings was decreased (Annett 1993). Attempts to replicate the Annett finding, measuring laterality using a peg-moving task, failed in 259 right-handed college students Cerone & McKeever 1990, showing if anything a slight advantage to extremes of right-handedness (in males, for some tasks). Similarly, Mayringer & Wimmer (2002) studied 530 boys aged between 5 and 8, and found no cognitive deficits associated with near-equal hand skill.

Thus, on the basis of concepts of handedness derived from preferences or skill measured on a peg-moving task, there does not appear to be a convincing relationship between lateralization of hand skill and cognitive function.

- Lefthandedness and survival

The debate has moved from simple questions of lefthanders having poorer cognitive performance, to the broader issue of survival. For example, rates of left-handedness decrease with age (Coren & Halpern 1991), suggesting that left-handers may be dying off faster than the right-handers, victims perhaps of a world built largely by and for right-handers.

However, this prevalence data has an alternative explanation. The change in social pressure over the last century, mentioned above, suggest rates of left-handedness should increase as the age of a sample decreases anyway. This latter conclusion has been supported by some impressive handedness datasets. Over 6000 individuals in a UK study (Ellis et al 1998), two groups of about a thousand Japanese students from before & after the second world war (Hatta & Kawakami 1994), 49,000 Swedish conscripts (Persson & Allebeck 1994), and over a million US males aged 10-86 (Gilbert & Wysocki 1992) all fail to show an increased mortality in lefthanders. Indeed, those studies with data at different ages show rather an increase in the prevalence of left-handedness over the 20th century. The US findings are also consistent with a well-documented shift in the teaching practices regarding left-handed pupils that occurred between 1915 and 1930. It seems there is more use of the left hand in younger people, even for tasks not so clearly subject to societal pressure (Hugdahl et al 1996).

Other studies have shown that left-handers more often claim special skill in art and mathematics, right-handers in music and verbal skills (Smith Meyers & Kline 1989). Given continuing social prejudice against left-handedness (as defining a minority) such findings are difficult to interpret, and their impact on survival is unclear.

- Pathological handedness

It is also suggested that some individuals use their left hand in preference to their right following injury (birth trauma, or more subtle pathology) to the part of the brain that would have otherwise made them right-handed (Satz 1972, Corballis 1978). This argument is developed by Coren & Halpern (1991), that the subtle pathology leading to lefthandedness is also associated with a maturational lag, although later work refutes this finding (Eaton et al 1996). Although 'pathological' lefthandedness may be significant in high risk groups such as extremely low birth weight infants (O'Callaghan et al 1993), it probably accounts for only for a small proportion of lefthanders in the general population (~5% or less - Bishop 1984 or Searleman, Porac & Coren 1989).

A similarly physiological but more over-arching theory is the 'Testosterone theory' of Geschwind & Galaburda (1985, 1987), which suggests that cerebral lateralization is determined by sex hormones. This could be seen as a hormonal equivalent of genetic theories implicating sex chromosomes, and appears to explain a wide range of handedness associations. However, implicating a causal agent that has such hugely diverse activity and interactions with other systems has led to profound doubts as to the whether this hypothesis is truly 'testable' (McManus & Bryden 1991).

Thus, the main findings to be explained by theories of aetiology remain the fairly extensive data on prevalence and inheritance. It remains unclear where selective pressure may be acting on hand preference today.

Genetic theories of handedness

- Annett - The right-shift theory (1964 - 2000)

Concept: Three categories of cerebral lateralization (plus developmental noise), via genetic restriction of the non-dominant hemisphere. 'Handedness' a correlate of this – measurable as a bivariate continuous measure of performance by side, or a threshold preference.

Undoubtedly the classic genetic theory of handedness, which has survived seismic shifts in its theoretical underpinnings and sustained invective (eg. Brand 1995 since its original publication in 1964 (Annett 1964). Despite this, it is claimed to account for a huge variety of findings in the areas of handedness and developmental disorders, including (most recently) autism and psychosis (Annett 1999).

It proposes a single autosomal gene, with two alleles, rs- and rs+. Thus an individual may be (rs--), (rs+-) or (rs++). The rs- allele has no effect on brain lateralization, but the presence of an rs+ allele restricts development in the right hemisphere in some way, thus promoting left dominance for speech and hand use (right-hand preference). After the initial proposition failed to convincingly model breeder-pair data, the theory was modified such that the effects of the rs+ allele could be additive (Annett & Kilshaw 1983); rs++ homozygotes are right-shifted further than rs+- heterozygotes. The handedness distributions of each subpopulation are then 'smeared' by fluctuating asymmetries, to give the overall findings. The relative proportions of genotypes are maintained in the population via a 'balanced polymorphism': a dynamic equilibrium between genotypes is achieved through ongoing selection, as heterozygotes have a slight functional advantage over homozygotes (Annett 1993).

From early on the peg-moving task (see chapter 2) was the preferred method of determining hand skill. This was chosen to 'avoid effects of practice at pen-holding' A laterality index is used to express the findings.

One clear finding was that plotting hand performance against laterality shows non-dominant hand performance increasing as one approaches equal hand skill, but dominant hand skill remains pretty constant regardless of hand skill differences (Annett 1992a). This was felt to suggest that dominance was being achieved through restriction of the non-dominant hemisphere, rather than a boost to the dominant hemisphere. This interpretation was reinforced when it was shown that planum temporale data showed a similar relationship between size and left-right size difference (Annett 1992b, although see chapter 7 for a critique of this interpretation).

Most recently the theory has been extended to propose an 'agnosic gene' that restricts one or other hemisphere at random (Annett 1999). If it restricts the otherwise dominant hemisphere, psychosis can result, and if it restricts an already restricted hemisphere, the result is autism. In the absence of an identified gene, the test is purely in the arena of epidemiological and family data, which the model fits quite well.

Over the years numerous investigators have failed to find support for the central predictions of the Right-Shift Theory (eg. heterozygote advantage not supported Cerone & McKeever 1999 etc.). Critics of the theory are many (see CPC 1995, vol 14(5) for a review), and perhaps are best summed under the general complaint that the theory has over the years managed to 'explain', post-hoc, almost any finding, any shape of relationship between handedness and a given outcome. Arguments to link handedness distributions predicted by the theory to a given outcome are inevitably post-hoc: although often neat, they are then un-testable. McManus (CPC review above) sums up that the "theory is derived from quantitative data, but only predicts qualitatively", and Bryden that "it is difficult to think of a result the theory would not claim to predict". It may be that ultimately the methodological bootstrapping used to construct the theory in the first place has left it, as a model, under-identified.

McManus (1985) also points out that, if handedness distributions do consist of several sub-populations of handedness type, the different tests used spread these out to differing degrees. Indeed, as the baffling fact needing explaining (and not ignoring) is why pen-holding preference is distributed in the way it is, Annett's focus on the relatively poorly-separated peg-board task is perhaps unfortunate.

More seriously, Annett's theory proposes that autosomal alleles can have an additive effect in homozygotes. The original 'non-additive' model was similar to that found for the gene identified as responsible for 'situs inversus' (Layton 1976). The current model proposes a quantitative trait locus, a single gene whose alleles can result in several discrete 'levels' of final expression. This added sophistication is a novel concept in genetics, and has yet to be convincingly demonstrated anywhere in the field of human genetics. Thus, until a gene is identified, we may never find a test the Right-shift theory can truly fail. This theory remains at the centre of ongoing debate.

- Levy & Nagylaki (1972) - a gene for side of speech dominance, and another for ipsilateral handedness

Concept: 'Side for speech dominance' as a binary category, and hand preference as an independent binary category referenced to this.

This theory takes as its starting point:
- most righthanders have left-dominance for speech, although a few have right-dominance
- 53% of lefthanders have left-dominance for speech, 47% right-dominance
- 35% of righthanders and 65% of lefthanders have no aphasia following left hemisphere damage.

Thus "hemisphere dominant for language" and "hand preference" are linked.

They propose a model with two dominant genes, with complete penetrance. One has alleles (L,l) controlling which hemisphere is language dominant, the other has alleles controlling whether hand preference is ipsillateral or contralateral to this (C,c). This simple model, given suitable allelic rates in the population, demonstrated a good fit for breeding ratios (ie. rates of lefthandedness in RR, RL & LL 'breeding pairs') and aphasia rates in their initial datasets. However, it has failed to fit larger, more recent datasets (eg. Hudson 1975), and has fallen into disrepute.

- McManus 1985 - 'Dextral' & 'Chance' alleles

Concept: Handedness as a binary preference category – right or left. Any continuous measures are just part of a normal distribution around the right (or left) mean phenotype.

The McManus theory is similar in some ways to the Annett theory, but differs in one key area - there is no suggestion of a genetic influence on the degree of handedness, merely direction.

(It is also important to note that the theory offers only a genetic explanation of handedness, and does not stray into issues of cerebral dominance for speech or other 'central' issues apart perhaps from a suggestion that preferred hand is centrally-mediated).

There is one autosomal gene with two alleles, a 'dextral' allele (D) and a 'chance' allele (C). Individuals can be (CC), (DC) or (DD). The chance allele leads to a 50:50 chance of being right or left-handed, so CC individuals are either right- or left-handed. The dextral allele homozygotes (DD) are all right-handed, 100%. The parameters for variation are then the allele frequencies, and how biased towards right-handedness heterozygotes (DC) are.

This theory differs from Annett's in how the phenotype is conceptualised. Annett sees the phenotype as a *'degree of handedness'*, spread out by fluctuating asymmetry, centred on zero, a shift from zero to the right, or two such shifts. Hand preference is then a 'threshold effect' on top of this. McManus sees *preferred hand* as the phenotype, 'degree of handedness' just being the performance of any human brain, again spread out by fluctuating asymmetry. In support of this he cites evidence that several handicapped groups (autism & fragile-X) show a loss of performance asymmetry, while retaining their hand preference asymmetry (McManus et al 1992, Cornish, Pigram & Shaw 1997). Although Collins (1985) found that mice can be bred for strength but not direction of pawedness, it is not unreasonable to suggest that humans are different from mice, in this and other respects.

Given the conceptual differences between the models, McManus rightly concludes that a direct comparison of the models is problematic (McManus 1985 Monograph). He then sets off to fit his model to a number of available datasets, and finds his model fits better than that of Annett. His model can also make quantitative predictions, and the examples he gives test satisfactorily. His model also does not predict any obvious relationship between cognitive function and measures of handedness, and he rejects Annett's findings that support the notion of heterozygote advantage (McManus Shergill & Bryden 1993).

Despite these apparent advantages, the subsequent literature has involved alternative methods of model-fitting, each favouring the relevant author, with little sense of determining which is 'correct' (eg. McManus 1995, Annett 1996). Given the ability to adjust the model parameters which include a noise term, it is again difficult to see how this model could be proved or disproved without an identified gene. The Annett Model seems to remain the more popular, presumably because of its much broader claims to explaining brain asymmetry rather than just handedness.

- Yeo & Gangestad 1993 - 'Developmental instability'

Concept: A single preferred degree of lateralization (plus noise), with homozygosity leading to fluctuating asymmetries. Effectively a distribution around the preferred degree ie. a continuous measure.

This theory proposes that a near-universal design of right-handedness is perturbed through 'developmental instability', to generate the distribution of handedness we see. They suggest that multiple genes control lateralization of the developing brain, these multiple genes protecting or 'canalising' its expression (van Valen 1978). However, heterozygote mating will lead to a fixed rate of homozygosity, a state of developmental instability, producing individuals who are more susceptible to environmental influences. Their brains are more likely to deviate from the plan, developing more 'fluctuating asymmetries' (deviance from population symmetries) than heterozygotes.

They found that individuals who were left-handed <u>or</u> extremely right-handed showed increased rates of lefthanded offspring (Gangestad & Yeo 1994), minor physical anomalies (MPAs) and specific fluctuating asymmetries (ref Yeo, Gangestad & Daniel 1993, Yeo & Gangestad 1993). They also demonstrated greater heritability of extremes of handedness than direction of handedness (Gangestad & Yeo 1994).

However, the theory does not make any clear predictions about exactly which aspects of development will be impaired in these individuals who demonstrate extremes of handedness. Research findings are not supporting the general thrust of the hypothesis eg. that individuals showing greater deviations from normal asymmetry are more likely to have a left-handed parent (McKeever et al 2000a&b).

- Laland 1995 - A 'gene-culture' model

Concept: Binary category of preferred hand, the right-handed category weighted in the population by a genetic factor and a cultural/environmental factor.

Laland observed:
- the similarity of monozygotic and twin concordance rates for handedness and the lack of convincing explanations for this
- the effects of cultural pressure on use of the left hand, but the inability of these to explain universal rate seen in all cultures

He proposed a model which is a synthesis, a 'gene -culture' model (after Feldman & Cavalli-Sforza 1976), where a child's 'genetic handedness' interacts with their parent's handedness to produce the observed phenotypic handedness.

Putting a term for 'probability of right-handedness' (genetic) and another for 'probability of using the same term as the parent' (culture), evolution of these over many generations can then be modelled mathematically to the point of stability between generations.

Results
- a genetic loading of 0.78 - everyone has a 0.78 probability of being right-handed
- a cultural loading of 0.14 - the probability of right-handedness increases by 0.14 if both parents are right-handed (mixed parents cancel each other's cultural influence out).

These are probabilities, on a binary categorical concept of handedness, similar to that of McManus, but with the added 'culture' term. Both are constants.

The model fits breeder-pair data and twin data well, although of course predicts no genetic variation at all, and does not address the small but consistent sex differences observed. The model makes predictions about handedness only, and does not seek to address other issues eg. cerebral dominance for speech.

- Discussion: Modelling handedness

Thus several contemporary theories of handedness can account for the main observations from a genetic perspective, although they employ different concepts of what the underlying asymmetry is. The models fit the observed data with varying degrees of power, in some cases depending on what method of model-fitting is used, which often varies by author. Aside from the complications of statistical model-testing, the differences between the underlying models can be obscured by the expression of their main effects (eg. 'preferred degree of handedness') in terms of a laterality index. Without a gene identified as responsible for influencing hand preference, it is difficult to see how this part of the field can advance.

There is as yet no coherent model that addresses why handedness is distributed in the manner it is in any testable form. The literature is awash with arguments from evolutionary biology as to 'why' righthand superiority was selected for (eg. arguments about shields held in the left hand better-protecting the heart in battle). However, these tend to fall foul of two main critiques:

The first is that the arguments are untestable. They refer to presumed phenotypes in the past in an environment important details of which are often missing. They presume knowledge of the cumulative consequence of a given phenotype in an environment inaccessible to experimental testing ie. the past.

Secondly, they tend to consist of "post-hoc-ery" of the worst sort, arguing from the position of 'knowing righthandedness must have an advantage'. In most instances a small amount of thought can provide similar arguments with the opposite conclusions. One can similarly question the notion that the hand preference is the primary asymmetry. It could be linked to some more fundamental asymmetry, be selected for by factors entirely internal to the species (such as sexual selection) and barely represent interaction with the environment at all.

Even if righthandedness has been selected for genetically, one then needs to account for lefthandedness' not disappearing altogether. Thus theories of handedness tend to account for a stable situation, however it arose in the first place. Indeed, if hand skill population biases have evolved, we may never be able to test why they did so. There may not be a meaningful 'why', as natural selection is blind to motivation (Dawkins 1999).

Schizophrenia - concepts and aetiologies - a brief summary

- The ancient world

Madness is mentioned in ancient texts such as the Bible and the Ayur Veda, and is discussed at length in 2nd century writings of Areatus the Cappadocian. However, while it is easy to translate 'descriptions of melancholia with episodes of extreme hilarity' into a modern diagnosis of 'bipolar affective disorder', these early accounts provide no clear pictures that could be considered schizophrenia. Indeed, it is only with the writings of Pinel & Haslam, in 1809, that such a diagnosis becomes reasonable.

- The nineteenth century

The nineteenth century saw a flurry of attempts to classify insanity. The first description identifiable with modern classifications was Morel's 1856 description of 'démence précoce' in a previously bright adolescent who lapsed into an isolated torpor. However, in 1896 Emil Kraeplin went beyond mere description, and divided psychoses (largely on the basis of outcome) into 'manic-depressive insanity' (fluctuating course with complete recovery between episodes), and 'dementia praecox' (progressive, chronic deterioration with no or only partial recovery, and an implicit deficit in cognitive function). The latter combined Kahlbaum's 1874 description of 'catatonia', Hecker's 1871 description of 'hebephrenia' and his own 'dementia paranoides'. Kraeplin felt that dementia precox would prove to be a disease with identifiable brain pathology.

- 'Schizophrenia' named

In 1911 Bleuler invented the term 'schizophrenia' (meaning 'split mind') to describe Kraeplin's group of chronic syndromes, although his understanding of them stemmed from the psychoanalytic schools rather than the neurological. His 'split mind' was the result of loosening of association between the various functions of the brain, and was primarily characterised by thought disorder, affective incongruity, autism and ambivalence, with the catatonia, hallucinations and delusions emphasised by Kraeplin very much secondary phenomena. Thus he could add 'simple' schizophrenia, characterised by the progressive breakdown of social and intellectual function in the absence of delusions or hallucinations, to Kraeplin's hebephrenic, catatonic and paranoid syndromes.

- Psychology vs. biology

Bleuler's 'schizophrenia' largely replaced Kraeplin's 'dementia praecox', especially in the US. This difference of conceptualisation was illustrated by the findings of a UK-US diagnostic project in 1972 (Cooper et al 1972) which found that New York psychiatrists were diagnosing schizophrenia much more often than their London counterparts. This was a consequence of the American's having a much broader view of schizophrenia than their European colleagues, and illustrated that the notion of psychosis either being obviously congruent with and secondary to a mood disturbance, or not, was not as clear-cut as many thought. Operational, 'checklist-style' definitions of the conditions were increasingly sought.

- Problems of definition

A prototype checklist was Schneider's 1957 'Symptoms of the first rank', a list of bizarre psychotic symptoms any of which would identify a patient as 'unequivocally schizophrenic'. Even at the time it was clear that they could also occur in epileptic and amphetamine psychosis, as well as manic psychosis. Opinions varied from "First rank symptoms => schizophrenia in all cases" to "Consistent mood change => affective illness +/- psychosis, regardless of the nature of the psychotic symptoms". Thus the Present State Examination (PSE, Wing et al 1974) places more emphasis on first rank symptoms, and DSMIV excludes cases more readily on the grounds of affective components. The reliability of a given interview schedule may be good *because* it is consistently failing to pick up important symptoms. Conversely, an interview may reliably distinguish between two forms of illness that in practice are all but the same. The validity of diagnoses derived from operational criteria and/or diagnostic interview schedules remains contentious. Even modern diagnostic schedules are poor at predicting outcome (Kraeplin's original validating criterion), with Schneider's first rank symptoms telling one almost nothing about prognosis (Mason et al 1997).

- Early biological findings

The search for a biological basis of the illness continued with Clouston (1890) examining palates of the general population (to detect defects of ectodermal development), and comparing them with those of 'criminals, the insane, epileptics, idiots and imbeciles, and cases of adolescent insanity'. Early work by Alzheimer (1897), Wernicke (1900) and others described histopathological changes in the brains of schizophrenics. However, in 1924 their methodology was called into question by Dunlap, who arranged comparison studies in the areas identified. He found no differences between cases and controls, following which finding scepticism clouded the field for decades.

Neuropathological research reflected technical advances, rather than testing of theories. In 1923 Lewis described peripheral vasoconstriction, in 1936 Kretschmer described changes in body build, in 1938 Gjessing described alterations in nitrogen metabolism, in 1962 Firedhof & van Winkel found a substance in the urine suggesting an aetiology centering on abnormal methylation of catecholamines, and so on. These and other findings would enjoy popularity, before either proving to apply only to atypical subgroups, or failing to be replicated altogether.

Neuroanatomical studies blossomed with the invention of the somewhat risky procedure of pneumoencephalography by Dandy in 1919. Although initial clear-cut findings (eg. in 1927 Jacobi & Winkler claimed that 18 of 19 schizophrenics studied had hydrocephalus) were not replicated, a series of large, well-conducted studies (eg. Huber 1957, Asano 1967) suggested strongly that ventricular enlargement was a consistent feature of groups of schizophrenic patients, although population variance meant such measures were not diagnostic for individuals.

- The rise of psychological aetiology

These neuroanatomical findings, the first firm evidence for a biological basis for schizophrenia, were all but ignored for much of the century. Much of the work was published in German, and associations between schizophrenia as a 'physical defect' and the horror of eugenics as applied in Nazi Germany led to a reluctance to pursue such work, and a feeling that it must be flawed. The two decades following the war also saw the rise of several highly-influential and purely psychological theories of schizophrenia aetiology (Fromm-Reichman (1948) and the 'schizophrenogenic mother', Bateson (1956) and the 'double-bind' hypothesis, and Lidz (1965) suggesting abnormal family interactions gave rise to schizophrenia). Barton (1959) in his book 'Institutional Neurosis' pointed out too that institutionalisation could account for much bizarre behaviour in perfectly normal people, and the more rigorous work of Wing & Brown (1961, 1970) demonstrated that some of the psychological and social deficits in schizophrenia were a consequence of the institutional environment.

- The paradoxical impact of neuroleptics

1952 saw the introduction of neuroleptic drugs by Delay & Deniker, with efficacy confirmed by the NIMH study of 1964. On this background much optimism developed that the institutions could all be closed and patients returned to the community, and that no particular provision would be required there, as medication could reverse symptoms that were caused by abnormal family interactions and sustained by institutional living. The need to find a biological, structural, genetic and/or developmental basis for the illness receded.

- Questions remain and multiply

However, by the 1970's the question about a biological basis was raised again, in the face of non-responders, deficits in individuals who had never been institutionalised, and difficulties in making testable hypotheses from the psychological theories. Previous work was re-examined, and technical advances have meant that the decades that followed have produced an ever-rising flood of structural and functional abnormalities detected in schizophrenics as a group, this time around proving reliable and consistent.

The findings cover almost every aspect of the human organism. They include findings from epidemiology, genetics, neurochemistry, neuropathology, neuroimaging, neuropsychology, developmental factors, social factors, life events and family factors. The sheer breadth of the field as it now stands is probably inevitable given its stubborn refusal to yield a single factor that allows the identification of an individual with schizophrenia, beyond the symptoms they complain of. A consequence of the vast array of data on differences means that current theories that claim to account for all of these are thin on the ground.

Numerous neural mechanisms have been implicated, include synaptic pruning (Feinberg 1983), myelination (Randall 1983, Weinberger 1986), recapitulation of phylogeny (Millar 1987), social cognition (Brothers 1990) and facial recognition (Grusser 1991). They all involve different brain areas, and are also theories of pathogenesis (the 'how?') rather than aetiology (the 'why?').

- Schizophrenia and cognitive function

Morel's original descriptions of 'démence précoce' set the scene for over a century of characterisation and investigation of schizophrenia as an illness characterised by cognitive decline. In a review of studies summarising data on over 1,000 patients with schizophrenia, Payne (1960) concluded that they had an average cognitive deficit of some 10 IQ points. Numerous studies have since confirmed that the illness is associated with cognitive deficits of many sorts (eg. Nelson 1990). The confounding effect of medication can be excluded by testing patients who have yet to be treated, although this restriction tends to exclude first-episode patients with more severe forms of the illness. Possible confounding by the variety of positive and negative symptoms experienced by patients are similarly difficult control for.

These issues have been satisfactorily addressed by studying individuals who later develop the illness, before the onset of symptoms. Such studies have confirmed that the cognitive deficits do indeed pre-date the illness onset. The deficits have been detected in childhood, decades before the psychotic illness manifests itself, as stable deficit of order one standard deviation below the rest of the population, on a variety of cognitive measures (Done et al 1994, Jones et al 1994). A study by Russell et al (1997), with standardised IQ measurement available from children attending a psychiatric outpatient clinic who later developed psychotic illnesses, failed to detect any significant differences between IQ measured in childhood and that measured in adulthood after illness onset. Although the sample under study is highly selected, this would seem to confirm that cognitive deficits are a stable characteristic of the brains of individuals who later develop the illness.

It should be noted that there is now an emerging literature that demonstrates similar findings in some patients with affective disorder (van Os et al 1997). There is perhaps a need to determine which cognitive deficits are illness-specific, before applying any findings to illness specific theories eg. of aetiology.

- Schizophrenia and laterality measures

Interest in this area arose initially from observations that early injury to the developing brain could affect shifts in handedness (Satz 1972). Handedness in schizophrenia was therefore investigated in the hope that this would provide evidence of early brain damage that might be implicated in the aetiology of the condition. Many studies have reported anomalous findings in handedness in schizophrenia. For reviews see Satz & Green 1989 (and update Satz & Green 1999); they note that consistency in the findings is hampered by great heterogeneity in the manner of measuring and reporting handedness.

It is concluded that schizophrenia is associated with a more variable and less completely lateralized pattern of handedness compared to the normal population (eg. see Cannon et al 1995). Extra methodological difficulties include the influence of possible selection biases in control selection, and questions over the generalisability of comparisons from the typical control groups eg.university students. These issues have been addressed by analyses in two of the UK birth cohorts (NCDS Crow, Done & Sacker 1996, NSHD Cannon et al 1997), which confirm an increase in mixed-handedness in children who develop schizophrenia as adults. In terms of handedness, these are all studies of hand preference; the Crow, Done & Sacker paper appears, at present, to be the sole comparison of hand skill in patients & controls.

A recent meta-analysis of the papers examining the relationship between schizophrenia and measures of lateralization more generally (eg. including measures of handedness, neuroanatomical asymmetries etc.) by Sommer et al (2001) also found a consistent decrease in the literature on reported asymmetry of the planum temporale and Sylvian fissures in schizophrenia.

Schizophrenia is associated with a shift in handedness away from the right-bias seen in the general population, and a shift from normal brain asymmetry, towards increased symmetry.

The Crow hypothesis

Tim Crow is a psychiatrist whose interest in schizophrenia arose from his work in neurophysiology (Crow 1968, Anlezark et al 1971). He proposed the highly influential division of schizophrenics into types 1 & 2 (Crow 1980), one an acute-onset florid psychosis, the other an insidious onset deficit state, an idea in which the origins of the neurodevelopmental hypothesis (see below) may be traced. After several years investigating then finally rejecting the theory that schizophrenia has a viral origin (Crow 1983), he returned to observations of structural differences in schizophrenic brains (compare Crow 1983 with Crow 1984, commentary in Crow 1993!).

He has proposed a theory to account for the findings mentioned above. Its origins lie in the writing of Crichton-Browne (1879) who proposed evolutionary formulations of the aetiology of insanity. It proposes that schizophrenia is an anomaly of the development of cerebral asymmetry (Crow et al 1989).

The theory claims to account for several crucial and otherwise incompatible pieces of evidence. Key among these are:
- prevalence rates for schizophrenia can be argued to be constant all over the world (Jablensky et al 1992), which effectively excludes most environmental agents from having any part to play in aetiology. Further, it can be argued that no exposure thus far examined has shown anything other than equivocal, small effects on rates of illness.
- there is clearly a heritable component to schizophrenia, although not explicable by simple Mendelian mechanisms (Gottesman 1991).
- 'psychosis is bad for you'; premorbidly, individuals who go on to develop adult psychotic illness show cognitive, social and personality deficits (Done et al 1994, Jones et al 1994), as well as having a major impact on fecundity(Gottesman 1991). If it has a genetic origin, the gene will have been selected out over successive generations, and if a mutation, should be considerably rarer than its observed 1% prevalence.
- brains of schizophrenics are less asymmetrical than the normal population (Crow 1989)

He proposes a single gene in the homologous region of the X and Y chromosomes that is responsible for an increase in structural and functional brain asymmetry. This increase in asymmetry has boosted the brain's language function to the point where our species-specific, abstract and infinitely generative language is possible (Crow 1995a, Crow 2000).

The 'price' paid for this functional boost, however, is that about 1% of the population will develop a psychotic illness. This 'price' paid by the human species is offset greatly by the enormous survival advantage conferred on the species by their superior language skills and all the consequences these have eg. organised agriculture, sewerage, space-shuttles etc. He also offers a formulation of schizophrenic symptomatology purely in terms of a breakdown in language function, if language is considered in its broadest sense.

The illness is seen as language function 'breaking down' in brains that are under-lateralized for this task. Thus groups of individuals with schizophrenia demonstrate brain function which is less asymmetrical than normals. The 'boosted asymmetry' characterising the human species may be found in numerous markers of brain asymmetry. Thus there may be many measures that show decreased asymmetry in schizophrenia (but see also Blyler et al 1997). Normal population variability is such that these will tend to be found only when studying groups, not individuals.

The hypothesis is at odds with the influential 'neurodevelopmental model' of schizophrenia aetiology (Murray et al 1992). This model, in some way arising from Crow's earlier observations of Types I & 2 schizophrenia, brings together observations about psychotic illness under a less specific proposal, ie. that schizophrenia is one possible outcome from the longitudinal developmental trajectory of the brain. A variety of exposures will each bring their own 'weight' to bear on neurodevelopment, abnormal genes, foetal and neonatal adversity all contributing to impair brain development. This impairment gives rise to the cognitive and social impairment seen in childhood (Done et al 1994, Jones et al 1994), before brain maturation in late adolescence and beyond precipitate the delusions and hallucinations characteristic of the adult illness. The neurodevelopmental model suggests that different amounts of different exposures will modulate characteristics of the final illness, for example more insidious onset and negative features due to a greater genetic weighting. Thus it acknowledges a clear rôle for environmental aetiological factors, unlike the Crow hypothesis, which proposes "One gene, and not much else"(Crow 1995b).

As with many over-arching theories involving large numbers of independent observations on a variety of aspects of the problem, there are numerous way-points where some will be able to join the proponent in leaping confidently to the next logical ice-berg, but others will not feel able to do so. For example:

- The Crow hypothesis places first-rank symptoms at the heart of the definition of schizophrenia, although they tell us nothing about prognosis (Mason et al 1997). This, of course, presupposes that schizophrenia is better defined in terms of prognosis, an equally moot point in the absence of aetiology.

- The Crow hypothesis formulates psychosis in terms of language function, when an understanding of the origins of language function and its mechanisms remain a matter of debate and evolutionary theorising ('speculation').

- The Crow hypothesis proposes an aetiological gene. Which everyone has. Quite aside from complex debates about the exact genetics, this concept in itself might seem rather opaque.

The Crow hypothesis remains highly controversial. For example, in a recent commentary by Trimble & Cutting (1998) the testability of the hypothesis is questioned, given the breadth of its scope. Also, they consider the centrality of first-rank symptoms to be a severe weakness, given a lack of a convincing historical record and more seriously a lack of heritability of these - see McGuffin et al. 1984, although Cardno et al 2002 substantially revise this view.

Although few authors at the present time feel able to 'sign up' to the hypothesis in its entirety, it nonetheless attempts to account for a large proportion of findings in what is now a hugely multidisciplinary field. Its strength lies perhaps less in its popularity or its comprehensive nature, as in its prospects for testability. For example, the suggestion that brain (and language) functional lateralization will be decreased in schizophrenia is now supported from a broad range of laterality investigations (review Sommer et al 2001).

From the perspective of this thesis, the key prediction is this: that cognitive function will be associated with measures linked to lateralization of language function. Further, the association should be that less than normal lateralization is associated with less than normal cognitive function.

Discussion

The question being asked is three-sided: What, if anything, are the relationships between cognitive function, measures of lateralization and schizophrenia?

Psychosis and handedness

There are several similarities between research into the origins and nature of handedness and psychosis:
- Both fields have been the subject of inconclusive study for over a century.
- The phenotypes, while 'obvious' to society, prove conceptually slippery
- Both are associated with language function
- Both have characteristics that appear unique to mankind

Although reports vary, there seems now to be a consensus view that psychotic illness is associated with a decrease in a wide variety of lateralization indices, whether referring to brain structure & function (for reviews see Gruzelier 1999, Sommer 2001), or handedness (eg. Cannon 1995, Claridge 1998, Green 1989).

Cognitive function and psychosis

Chronic psychotic illness as an adult is associated with cognitive deficits in childhood that are characteristic in groups, although the effect sizes are too small to identify individuals (eg. Done et al, Jones et al 1994).

Cognitive function and handedness

That cognitive function is not significantly correlated with preferred hand has been demonstrated many times (eg. Douglas et al 1967, Hardyck et al 1976, Clymer and Silver 1985). However, studies looking at finer distinctions than mere right or left preference do suggest some intellectual handicap associated with mixed handedness (Annett 1970, Calnan & Richardson 1976), although effects are small, and often inconsistent.

Given the correlation between preference indices and performance indices (Bishop 1989), to predict an association between performance lateralization indices and cognitive function is perhaps not unreasonable. Thus any explanation will have to account for this seeming contradiction - an association between cognitive function and lateralization measures, and possibly with preference measures, but no association with preferred hand.

The McManus theory predicts no relationship, and that any variation is noise, confounding or measurement error. The Annett theory does predict 'heterozygote advantage', which should manifest as a fall-off in cognitive performance at extremes of right-superiority (as defined by laterality indices), although how to convert this into a testable, quantitative, prediction is unclear. The Crow hypothesis predicts a drop in cognitive function in brains that are less asymmetrical, for any degree of overall performance. The latter is perhaps the most specific and testable. No theories are sufficiently quantitative on this point to suggest an effect size.

Chapter summary

A variety of models attempt to account for the distribution of hand preference and skill from a genetic and environmental perspective. The same is true for schizophrenia. Some make predictions about the relationship between measures of lateralization and performance. However, perhaps because of practical and theoretical problems, these relationships have yet to be satisfactorily clarified. The variety of concepts employed in different models also makes comparison difficult.

Handedness in humans cannot be accounted for as a fluctuating asymmetry. It must either have been selected for, or be linked to some other facility that has been selected for. The reason for this selection could well be an association with cognitive function, although no hypotheses suggest an expected effect size. This association may still be measurable today, if we can keep the concepts clear and avoid methodological confounding.

Chapter 4: The thesis

The position taken in this thesis

The position taken in this thesis is that what people mean when they talk of 'lateralization', while appearing intuitively strong is potentially very weak and ambiguous. As a condensation of two measures, from right and left sides, without a clear hypothesis of origins it loses meaning, and this has confused the field.

The word 'lateralization' has such a wide variety of potential meanings that comparison and interpretation of findings between studies can become impossible. 'Explanatory' reasoning can too easily become circular, with explanations couched in terms of natural selection easily going either way, to suit a given hypothesis. There is little understanding of how 'programmed' asymmetries (as opposed to fluctuating ones) come about, or are manipulated. Indeed, there are no satisfactory models elsewhere in genetics of gene expression influencing quantitative traits.

Support for this thesis derives from an examination of *laterality* in nature that emphasises the essentially unknown processes from which population asymmetries derive. This calls for extreme caution to avoid unstated assumptions about origins. An examination of *laterality indices* also suggests that, despite their superficial simplicity, they are mathematically fraught, with great potential for misinterpretation.

It follows that an initial exploration of laterality data that avoids these pitfalls should be informative and less confusing.

The context

There is a huge array of research data on handedness and lateralization, stretching back over many decades. In the hope of making things more manageable, a 'map' of research in laterality is offered (figure 1).

The structure of the diagram isolates broad islands of interest - areas that are investigated. This map includes:
- the key relationship between aetiology and brain development
- the relationship between lateralization in the brain, and functional lateralization of peripheral functions
- the notion that peripheral lateralizations might effect cerebral lateralization, as well as (more obviously) vice-versa
- the notion that adult outcomes might be mediated by the direct effects of lateralization on cerebral function, as well as indirectly via effects of peripheral lateralization.

Understanding of the exact nature of the relationships represented by arrows varies considerably. There appears to be as yet no clear understanding of the processes that control the lateralization of the developing brain, or the nature of the connection between the structural and functional lateralization seen in the brain itself ('proximal phenotypes'), and peripheral functions ('distal phenotypes'). The central position on the map of these two connections illustrates how potentially key they are to a model of the aetiology of the distribution of handedness seen in the human population. Much of the data gathered so far explores each region separately, in the hope of modelling just that outcome, rather than exploring these connections.

The analyses in this thesis

This thesis examines some of the issues raised thus far, most explicitly addressing two areas that are currently unsatisfactory, and need clarification:
1. The fact that laterality indices are easily misinterpreted, leading to false assumptions about the distribution of laterality measures in the population.
2. It is impossible to say, from an analysis involving laterality indices, whether or not a previously-recorded drop in cognitive performance in functionally more-symmetrical individuals is due to over-representation of handicapped individuals.

Methods of analysis are developed to overcome these problems. These methods are then used in exploratory descriptions of both the distribution of laterality measures in the population and their relationship to cognitive and other measures, as well as a tentative exploration of this data in premorbid cases of psychosis.

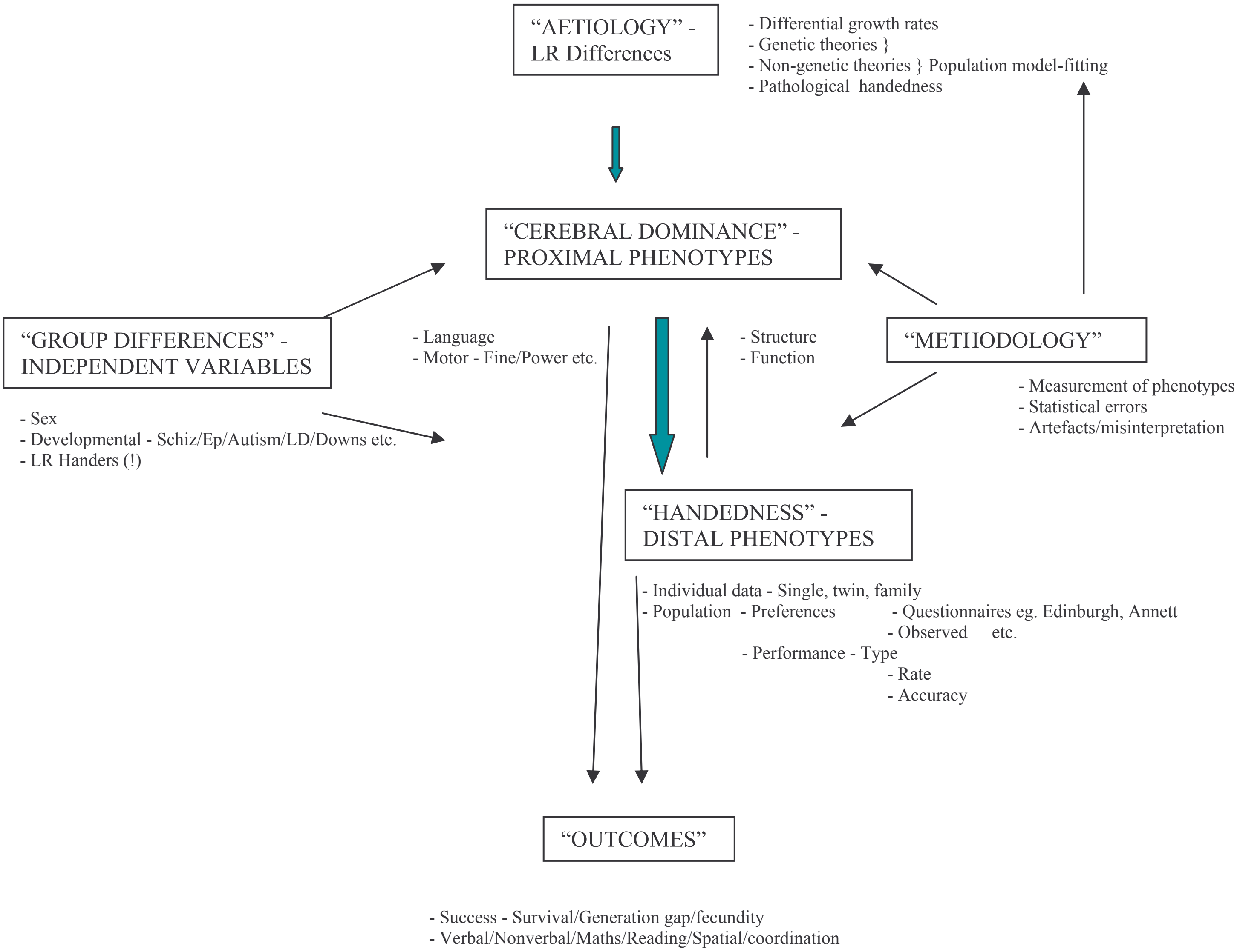
Results will describe the relationship between simple measures of functional lateralization and other brain function. This can be seen as both examining the connection between distal phenotypes (hand skill) and outcomes, as well as the connection between proximal phenotypes (cognitive function) and distal phenotypes (hand skill). It will also be seen whether simple descriptive figures of these relationships illuminate the central contradiction, that cognitive function is predicted to associate with measures of functional lateralization, yet is not associated with preferred hand.

Finally, by including 'real' success variables, such as measures of income, social class, and even psychiatric illness and schizophrenia, it is hoped that something can be said of the validity of any findings ie. that any associations found apply not just to laboratory tests, but have real impact on psychological development.

Chapter summary

It is briefly stated, with the aid of a 'map' of research approaches to lateralization, where the weaknesses in the field are. It is then stated how the analyses in this theses may address these.

Figure 1: LATERALIZATION RESEARCH
- A MODEL



Chapter 5: The NCDS & BCS70 UK birth cohorts

Introduction

The data analysed in exploration of this thesis arise from two UK national birth cohorts. We will examine:
- why use birth cohort data to support this thesis?
- why use large sample data to support this thesis?
- the two UK national birth cohorts used (NCDS & BCS70), and
- the variables analysed.

Why use birth cohort data?

The UK birth cohorts consist of longitudinal data on a large sample. The advantages of these two aspects of the data will now be considered.

Why use longitudinal data?
Longitudinal data is "absolutely indispensable" for examining four broad types of research question (MRC 1992):
- study of developmental processes
- testing causal hypotheses about risk/protective mechanisms
- studying the natural history of disorders, and
- studying the incidence of disorders in relation to some specified circumstance (eg. a life event, or social/environmental change).

In the terms of this thesis measures of handedness can be seen as indicators of a fundamental neuropsychological variable, and cohort data can therefore shed light on the developmental process it reflects.

More specifically, there are a number of merits intrinsic to longitudinal data over case-control data that apply to the analyses carried out.

Exploring unexpected risk factors
Retrospective data cannot be use to study risk factors involving variables that are not known to the respondent or his family and are not routinely or easily found in records. This issue is relevant to handedness data in any other form than preferred hand for writing (even in this instance, seldom recorded routinely). It can also be seen as relevant in a field where the 'true' formulation of the 'exposure' is unclear eg. is it useful to know preferences, or should we consider performance differences only?

Avoiding retrospective attribution bias
When studying antecedents of such negative outcomes as serious mental illness, recall of poorly-documented 'exposures' can become highly confounded by recall bias. For example, it is characteristic that people explain away an accident that was their fault in terms of the bad fortune that had dogged them that day, whereas prospective gathering of data would suggest no obvious difference between that day and any other. Similarly, recall of characteristics of children who developed schizophrenia in adulthood is susceptible to numerous biases related to knowledge of the negative outcome.

The key is data gathering prospective of the outcome of interest, which avoids any bias that could result from knowledge of the outcome, positive or negative. In this analysis, it should be remembered that lefthandedness is seen as an abnormality, historically in this and contemporaneously in other cultures (see chapter 3), and therefore recall of handedness as a child could be biased.

Asking "What happens next?"
Third, testing a causal hypothesis requires data on intra-individual change, over time or in association with a risk factor. Despite the existence of data on handedness at different ages in this cohort, the data types differ - hand preference is categorised differently at different ages, and hand performance only measured at one age. Hence, for this thesis, this feature of cohort data is not capitalised on, although developments in structural equation modelling may allow for this in the future, a topic returned to in the conclusions in chapter 10.

Exploring unknown outcomes
Only longitudinal data from multi-purpose cohorts provide an adequate opportunity to detect unexpected adverse outcomes, and provide an adequate assessment of the overall level of risk when the risk affects multiple outcomes. For example, smoking is now known to impact on numerous physical outcomes beyond respiratory illnesses. The latter example illustrates that diverse outcomes do not necessarily mean non-specific effects; the risk mechanisms are specific and well-understood, but are of more than one type. Handedness may be associated with outcome in just this fashion; characteristic constellations of outcomes may be observed to result from characteristic neuropsychological function, in turn reflected by handedness.

Exploring unexpected associations
Population data have many advantages for the detection of so-called heterotypic continuity ie. discontinuity of exposure & outcome 'type'. For example, most longitudinal studies of juvenile delinquency have focussed on adult criminality or antisocial personality disorder as outcome. Data from the NCDS has shown that child conduct disturbance predicts adult emotional disturbance in adult life almost as well as child emotional disorder does, opening up a range of new research questions about mechanisms involved. The association of handedness measures and adult psychological function might be seen entirely as an example of heterotypic discontinuity.

Introducing 'new' outcomes
In order to study outcomes not seen as part of the original study, a design known as a 'follow-back' study may be employed, as described in the next chapter. Assuming that both cases and cohort members are relatively easy to identify, the approach allows study of specific, tightly-diagnosed conditions in the context of large volumes of prospectively-gathered populations of data. The follow-back process employed here is described in the next chapter.

Problem: Dated measures
A frequent criticism of longitudinal data is complaints about the dated concepts inherent in data recorded many years previously. While some measures, such as height or weight, are robust to changes over time in concepts of measurement, others, such as the scales of socialised behaviour or social class, have evolved over the years, possibly to the point where meaningful comparison of these original measures with current formulations of the concepts can be difficult. Indeed, the social context in

which the study is performed also moves on over time, with all the potential for confounding that environmental and social change brings with it. Similar key findings in cohorts from different epochs would at least provide some reassurance.

Problem: Inconsistent measures

Any analysis over time is going to be problematic if the measures at different times are not adequately equivalent. In the area of handedness, care must be paid to exactly how a measure of handedness or laterality was made on each occasion, before assuming one can then use the data to examine changes over time. A recalled measure of left or right-hand task preference cannot be assumed to be giving the same result as an observed one (see chapter 2).

Why use Large Sample data?

The use of smaller samples often allows more intensive data collection, using standardised methods and often requiring highly-trained investigators, producing high-quality data. The benefits of examining a large sample at 'lower resolution' must therefore be clarified.

Characterise the population before exposure

Large samples are needed if one wishes to identify and study a sample before exposure to a risk factor. For example, if only 10% of the population were exposed to the risk factor, a sample of 1000 would be needed in order to have 100 exposed individuals (a typical minimum sample size in order to determine a meaningful increase in risk). This example applies to the 10% of individuals are left-handed, and who we might wish to consider as a group. When performing by-group analysis examining rarer outcomes (eg. schizophrenia), even populations ten times as big are barely adequate.

Avoid sampling bias

Samples consisting of entire populations also have the advantage of avoiding sampling biases of most kinds. In birth cohorts the most obvious bias is one of a highly-selected birthdate, leading to a bar on examining seasonal effects. This is ideal when examining a variable such as handedness, which has often been examined in selected, accessible groups such as psychology students.

Problem: Limitations on types of measures

National cohort studies are often-criticized for their reliance on paper-and-pencil tests and self-report. However, while this is a real limitation, in a cohort setting it can be addressed at least partially, by recording similar data from multiple sources (teachers, health visitors, subjects), and at multiple time-points. Variance in the latter can of course then be a potential confound for analyses over time, especially in categorical variables. In a birth cohort, the data-gathering lies somewhere on the spectrum of data quality between the multiply-sourced and simplified data fed into for meta-analyses, and the precisely-standardised data gathered by trained specialists in smaller, individual studies. There will have been local differences in interpretation and procedure, but testing is at least carried out according to a centrally-defined rubric, at a similar time across a national health service.

Problem: Attrition and potential bias
The practical difficulties associated with following up large samples over time mean that attrition is more of a problem. Whether this biases the sample with respect to the outcomes under study needs careful examination.

Larger sample sizes give greater confidence
Finally, large samples also bring the obvious advantage of greater statistical resolution to most analyses. In addition, a hypothesis suggested by findings from an exploratory analysis in a random subset of a large dataset can then be tested by a confirmatory analysis in another subset.

However, the impressively small p values that can characterise large sample analyses cannot of themselves make trivial effect-sizes suddenly meaningful. Data quantity will only ever partially address problems of data quality and face validity..

The 1958 National Child Development Study (NCDS)

Population
The National Child Development Study (NCDS) began life as the 1958 Perinatal Mortality Survey (PMS). Sponsored by the National Birthday Trust Fund, this was designed to examine social and obstetric factors associated with stillbirth and infant mortality. It covered about 98% of all births in England, Scotland and Wales during the week 3-9 March 1958, representing over 17,000 babies (Butler & Bonham 1963).

It was the second in a series of three such perinatal studies, the others being based on a week's births in 1946 (Douglas 1964) and 1970 (see below). Each has formed the basis of a continuing longitudinal study. At the time of the PMS the perinatal mortality rate (stillbirth or death within 7 days of birth) was 35 per 1000 births, and the study demonstrated, for example, that the risk of perinatal death was 50% higher than average for the fifth or subsequent baby, and was 30% higher than average if the mother was a heavy smoker (Butler & Bonham 1963).

Strong representations from Dr Pringle (Director of the National Children's Bureau), Professor Butler (an eminent paediatrician), and Professor Wall (then director of the National Foundation for Educational Research) were made to a Government committee set up to look into primary school education (the Plowden Committee). Following this the Department of Education and Science agreed to commission the National Children's Bureau to collect information on all these children when they were seven. The study became known as the National Child Development Study (NCDS), and the first major publication appeared as an appendix to the Plowden Committee report (Pringle et al 1966). The cohort was thus established for longterm study (table 1).

Short-term:
- To study the educational, behavioural, emotional, social and physical development of a large and representative group of British children in order to gather normative data; to investigate the complex interrelationships between the many facets both normal and deviant, of children's development; and to report the incidence of handicaps with the provision currently being made.

- To utilise the uniquely comprehensive perinatal data, already available, in an evaluation of the relationship between conditions during pregnancy and at birth, both medical and social, and the development of children in all aspects at the age of 7 years.

Long-term:
- To explore the constancy and change in the pattern of children's development longitudinally, and to investigate the associated educational, environmental, educational and physical factors.
- To follow the progress - over a long period - of those children who at birth might be considered at risk in order to evaluate possible latent effects; and also to examine any post-natal factors, environmental, educational, or medical, which may minimise handicap.
- To identify and follow progress of children who at 7 years of age are already handicapped or showing signs of difficulty: those who because of adverse social or other circumstances might be considered at risk of becoming educationally backward or socially deviant; and those who display exceptional talent or aptitude.
- To evaluate the efficiency of medical and educational provision for handicapped, deviant, and exceptional children.
- To identify groups of children of special interest, including many of those identified under (c) and (d) above, so that intensive studies may be mounted by expert teams. This would permit much more detailed and comprehensive investigation of the factors involved against a backcloth of the necessarily cruder data gathered in the follow-up of the whole cohort.

Table 1: Aims of the NCDS as instituted in 1964 (taken from Shepherd 1985)

Subsequently, surveys of the entire cohort were carried out at ages 7,11,16, 23, 33, (table 1) and although at the time of writing figures were not available, most recently at 42 (Davie et al 1972, Fogelman 1983, Ferri 1993, Bynner et al 2000). At the age of 33, a special study was also undertaken of the children of one third of the cohort members, including assessments of the behavioural and cognitive development of approximately 5000 children. There have also been surveys of sub-samples of the cohort, the most recent at age 37, when information was collected on the basic skills difficulties of a representative 10 per cent sample (Bynner & Parsons 1997).

PMS 1958 Birth	NCDS1 1965 7	NCDS2 1969 11	NCDS3 1974 16	EXAMS 1978 20	NCDS4 1981 23	NCDS5 1991 33
17,733(a)	16,883	16,835	16,915	16,906	16,457	16,455
Parents	Parents	Parents	Parents			
	School	School	School	School		
	Tests	Tests	Tests			
Medical	Medical	Medical	Medical			
		Subject	Subject		Subject	Subject
			Census		Census	
						Spouse/ Partner
						Children
17,414(b)	15,468	15,503	14,761	14,370	12,537	11,407

Table 1. Coverage of sweeps from birth to 33 in the NCDS.
(a) Target sample (b) Achieved sample

In addition the cohort was augmented by including immigrants (born in the relevant week) into the target sample for the first three follow-ups at ages 7, 11 & 16, identified from school registers. No new immigrants have been added since the sweep at 16 in 1974.

From its original focus on circumstances and outcomes of birth, the NCDS has broadened in scope to chart all aspects of health, educational and social development of their subjects, including later transitions to adult life, such as leaving full-time education, entering the labour market, setting up independent homes, forming partnerships and becoming parents. In 1985 responsibility for the NCDS passed from the National Children's Bureau to the Centre for Longitudinal Studies (CLS), formerly the Social Statistics Research Unit at City University. In 1991 responsibility for the 1970 British Cohort Study (BCS70, see below) was also transferred from Bristol University to the CLS. A Forward Plan for both cohort studies was developed, also taking into account the sequencing of Britain's third cohort study, the 1946 National Survey of Health and Development (NSHD). Funding was initially made available by the Economic and Social Research Council (ESRC) to sweep BCS70, which had not been directly examined for thirteen years, but this was later extended to the NCDS. The ESRC provided half the funding, and Government departments (coordinated by the Office of National Statistics (ONS)) contributed provided the other half, the lions share coming from the Department for Education and Employment, and the rest from the Department of Health, Department of Social Security, the Home Office, the ONS themselves, the Scottish Office and the Basic Skills Agency.

Hence between November 1999 and April 2000, the most recent sweep of both NCDS and BCS70 cohorts combined, took place across mainland Britain. A move to cross-cohort methodology and organisation has thus characterised the development of UK research into the life course in the new millenium.

The patchwork of funding from different government agencies described above has characterised both NCDS & BCS70 funding over the years. This has provided a variety of potentially conflicting pressures on the content of each sweep, in contrast to the continuous central funding made available for the NSHD. This is manifest in the lack of continuity of measures between sweeps, and the absence altogether of some measures of great potential interest eg. blood pressure and lung function.

Despite these problems, thanks to the determination and drive of the individuals concerned with the NCDS it has been followed up reasonably consistently over the years, and seems set to continue in this way.

Considerations of data collection, quality and attrition will follow in the context of the individual measures used in subsequent analyses.

Sources of data - Birth:
Information came from questionnaires completed by the midwife in attendance at the delivery, referring to all available notes and after interviewing the mother.

Distribution of the questionnaires relied heavily on the complex administration of the National Health Service, with Regional Hospital Boards and Boards of Governors of Teaching Hospitals distributing to maternity departments, and Medical Officers of

Health distributing to domiciliary midwives. Questionnaires were also distributed to units where babies might be admitted (eg. premature baby units) or die after birth.

Completed forms were checked by matrons, midwifery superintendents, or midwife supervisors, and returned to the Medical Officer of Health for the county or county borough area in which the births or perinatal deaths had taken place. Here they were checked against official notifications. Missing questionnaires were sought and deficiencies rectified. With facilities in every health region for the survey director to meet personally with those providing the maternity and newborn services, maximum cooperation was obtained. 98% of all births for this week were included in the study.

Mother and father's social class was recorded from this interview with the mother. Father's social class was used in subsequent analysis.

The first three follow-ups (7, 11, 16)

After piloting in a number of health authorities, interview schedules and questionnaires were distributed to local health authorities and local education authorities, who arranged distribution to medical officers and health visitors (medical examinations and parental interviews), and schools (head teacher & class teacher questionnaires on each subject). They also arranged for their collection and return to the National Children's Bureau. At 11 and 16 the subjects themselves were also asked to fill out a questionnaire at school.

Follow-ups at 23 & 33
These two sweeps differed from those previous in two areas, that information was obtained directly from the subject, and that they were interviewed by a professional survey census research interviewer.

Measures available in the NCDS cohort

The measures in the NCDS dataset available for the subsequent analyses are summarised in Table 2.

Age	Measure	Source	Data
0	Father's social class	Interview with mother by midwife	Husband's occupation, re-coded as social class
7	Father's social class	Interview with mother by health visitor	Husband's occupation, re-coded as social class
	Reading	Test at school (1)	Score 0-30
	Mathematics	Test at school (1)	Score 0-10
	Handedness	Interview with mother by health visitor (a):	
		Does the mother think the child is..."	R - L - Mixed R&L - Don't know
	Laterality tests	Medical examination tests (o):	
		Hand: Throw a crumpled paper ball, Draw a cross	R (only) - L (only) - L&R used - Could not test
		Foot: Kick crumpled paper ball, Hop on one leg	R (only) - L (only) - L&R used - Could not test
		Eye: Look through rolled paper tube, Look through hole in a card	R (only) - L (only) - L&R used - Could not test
11	Father's social class	Interview with mother by health visitor	Husband's occupation, re-coded as social class
	Reading	Test administered at school (1)	0-35
	Mathematics	Test administered at school (1)	0-40
	Verbal & non-verbal ability	Test at school (1)	Score 0-40
	Handedness	Interview with mother at medical examination (a):	
		"Is your child...."	R - L - Mixed R & L - Don't know
		"Which hand does your child write with?"	R - L - Don't know
	Laterality tests	Medical examination tests (o):	
		Hand: Throw a ball	R - L - Not examined
		Foot: Kick a ball	R - L - Not examined
		Eye: Look through a rolled paper tube	R - L - Not examined
		Mark squares in one minute	0-200 for each hand
		Pick up 20 matches	10-99 seconds for each hand
16	Father's social class	Interview with mother by health visitor	Husband's occupation, re-coded as social class
	Reading	Test administered at school (1)	0-35
	Mathematics	Test administered at school (1)	0-31
	Handedness	Individual questionnaire (a): With which hand do you write best?	R - L - Equally well with either
23	Social class of subject	Subject questionnaire	Occupation re-coded
	Age at first child	Subject questionnaire	Derived from dob 1st child
33	Social class of subject	Subject questionnaire	Occupation re-coded
	Number of children	Subject questionnaire	0-9
	Highest qualification acheived	Subject questionnaire	Derived from list of qualifications

Table 2: Sources of data in NCDS

(1) Tests of intellectual performance:

7: Reading: Southgate Group Reading Test: A test of word recognition and comprehension particularly suited to identifying backward readers (Southgate 1962)

7: Mathematics: Problem Arithmetic Tests (Pringle et al 1966)

11: Reading & Arithmetic/Mathematics Tests: Reading comprehension test constructed by the National Foundation for Educational Research in England and Wales(NFER) specifically for use in this study.
11: Verbal & Non-verbal Tests: Scores from General Ability Test (Douglas 1964).
16: Reading & Arithmetic/Mathematics Tests: As used at 11.
Copies of tests used in NCDS follow-ups are available from:The Supplementary Publications Scheme,British Library(Lending Division)Boston Spa,Yorkshire LS23 7BO,quoting reference no. SUP 81013.
(a), (o) Laterality measures:
(a) These are answers to questions, either verbal (from examining doctor) or on a questionnaire ie. the information is recalled by the subject, or their mother.
(o) These are observed behaviour, in the context of the medical tests
- at 7 the child was asked to perform various tasks, and their actions recorded
- at 11 various tasks were observed, including a box-marking task in which the number of boxes ticked in a minute by each hand, and the time taken by each hand to move 20 matches individually from one matchbox to another, was recorded.

Measures used in the analyses

The purpose of the analyses has been to examine outcome with respect to handedness measures. This hypothesis suggests that measures of handedness (the 'distal phenotype') reflect the organisation of the cerebral processing behind them (the 'proximal phenotype'), and that differences in this overall organisation are reflected in differences in psychological performance between individuals.

The measures used in the analyses are related to the 'exposure', handedness measures, and a variety of outcomes related to psychological performance. The outcomes considered are 'successful' psychological performance, as reflected in educational and employment success, and fecundity, and problematic psychological performance as measured by admission to psychiatric hospital, psychotic illness and schizophrenia (see chapter 3).

Associating certain outcomes with 'positive selection pressure', while superficially attractive if looking for explanations for selection of these features, risks becoming a self-fulfilling prophecy. Factors that make one 'successful' in the eyes of society, such as education or a well-paid job, do not necessarily mean they increase your chance of reproducing and passing your genetic loading on to the next generation. Indeed, while all these measures are highly correlated with IQ, the most rapidly-reproducing humans are not those with the highest IQ. Similarly, higher social class, or the greatest ability to rise through social classes do not necessarily reflect reproductive success. Even the concept of fecundity is a combination of age at firstborn, number of children *and* their rate of survival, and as such is not clearly accessible from the data in this cohort. More fundamentally, even if one were to measure fecundity with certainty, whether the factors that contribute to this today are related to those that were important throughout man's evolutionary history (ie. between 2 million and 50,000 years ago) is surely a matter for the speculative and frequently untestable debate beloved of evolutionary biology.

However, as can be seen in Table 2, the preference and performance data was collected inconsistently between sweeps, making examination of changes over time problematic (see discussion below). Further, measures were needed that were available in both cohorts. Thus it was decided to restrict the analysis to the hand preference measure of interest (hand used for writing), the performance measures

(box-ticking & match-picking), and five simple measures of adult psycho-social performance, or 'success' by the age of 33
- social class
- the difference between this and the social class of father at birth (ie. some notion of 'self-improvement')
- weekly income
- highest educational achievement, and
- number of natural children.

An exploratory exercise was envisaged, so this limitation on the number of measures was also hoped to limit the final figures to a manageable number.

Attrition
The numbers of subjects in the cohort has decreased over time. There is the possibility that this has biased the sample over time. How representative is the responding sample of the original cohort, and thereby of people of that age in Britain?
This question can be addressed in the manner only available to longitudinal studies; respondents and non-respondents can be compared on measures from earlier sweeps. The second answer comes from comparisons with similar datasets eg. General Household Census data. Such analyses have been performed elsewhere, and overall " the achieved sample does not differ from the target sample to any great extent" (Appendix 1: Ferri 1993) on a wide variety of measures (eg. social class, educational scores, housing etc.). For the purposes of this thesis, a preliminary analysis was carried out to compare the distribution of handedness indicators in their sample of origin, compared with those individuals examined at 33 (table 3). Although in such a large dataset significant differences are easy to achieve, overall there is little over- or under-representation of groups in the surviving sample; the differences in these response bias percentages on these variables are about half of those (acceptable) biases seen in measures of housing, education and health.

	Target %	Achieved %	% Bias
Left hand @7	10.51%	10.28%	-2.2%
Left hand @11	11.55%	11.32%	-2.0%
Left handed @16	11.30%	11.56%	2.3%
RH ticking <100 boxes	64.48%	63.55%	-1.4%
LH ticking <100 boxes	90.95%	90.65%	-0.3%

Table 3. Response bias in NCDS5 with respect to handedness variables.
(% Bias = ((NCDS achieved%-Target %)/Target %) x100)

The 1970 British Cohort Study (BCS70)

Population
The 1970 British Cohort Study (BCS70) also began life as a survey of perinatal mortality with a more strictly medical focus, the British Births Survey (BBS), sponsored by the National Birthday Trust Fund and the Royal College of Obstetricians and Gynaecologists. It began by collecting data on about 97% of the births in the United Kingdom (England, Wales, Scotland and Northern Ireland) who

were born between 5th and 11th April 1970, some 17,198 individuals. However, from the outset there were suggestions it should continue as a cohort study, and attempts have been made to follow up the entire cohort at ages 5, 10, 16 and 26, and most recently 30.

As with the NCDS, over its life the sweeps have broadened in perspective, adding to the original medical data at birth, physical and educational data at age five, these and social data at age ten and sixteen, and economic development data at 26 (Table 2). The five and ten year surveys were carried out by the Department of Child Health, Bristol University, named the Child Health and Education Survey (CHES), reflecting its educational perspective. The sixteen year survey ("Youthscan") was carried out by the International Centre for Child Studies, as was the postal questionnaire survey at 26.

Sample surveys also took place. The British Births Child Survey of 1972/3 examined all twins, low birthweight and postmature births, and a random ten percent of the original cohort. The South-West Region Survey carried out at the same time included 95% of cohort members living in the south west of England or Glamorgan, South Wales. These attempted to close the large developmental gap between birth and five years. In 1977 non-responders to the 5 year survey were traced and interviewed, to assess effects of non-response. In 1992 the SSRU employed research interviewers to examine influences on the transition from full-time education to employment, and gather information on the prevalence and origins of literacy and numeracy problems in a sample of 1,650 cohort members.

As with the NCDS, the cohort was augmented by immigrants to Britain born in the target week in the 1975 and 1980 sweeps. Subjects from Northern Ireland, included at birth, were dropped from any of the subsequent sweeps.

BBS	CHES	CHES	Youthscan	BCS70
1970	1975	1980	1986	1996
Birth	5	10	16	26
				13,500(a)
Mother	Parents	Parents	Parents	
		School	School	
	Tests	Tests	Tests	
Medical	Medical	Medical	Medical	
		Subject	Subject	Subject
17,198(b)	13,135	14,940	11,628	9,003

Table 4. Coverage of sweeps from birth to 26 in BCS70.
(a) Target sample (b) Achieved sample.

Sources of data - Birth

Table 4 above summarises the data sources at each sweep. At 5, 10 and 16 local education authorities and regional councils (Scotland) were asked to identify all children with relevant dates of birth on school registers. From this data and that already extant from previous sweeps, a study register was created. Changes of name and/or address made the process of resolving this register difficult; where entries could be resolved across time and space to a single individual their Central Survey Number (CSN) was retained, but in other cases a new CSN was allocated and retained unless or until matching was accomplished.

Study coordinators were appointed in each region to receive and distribute Educational Packs to schools, and return them once completed. District health authorities and health boards (Scotland) were asked to appoint a medical and/or nurse coordinator to arrange for each study member a home interview and medical examination to complete their Health Pack. During the study, family practitioners committees and health boards (Scotland) were asked for information on any children on their lists with relevant dates of birth, thus augmenting the register.

The sweep at 16 encountered an unforeseen and prolonged teachers strike. The National Union of Teachers declined to recommend the Education Pack of the study to its members (although in the event no action was brought against any teacher who cooperated). Questionnaires and tests were re-designed for self-completion, but this delayed the sweep from its target age, a sweep at 15½ before the minimum school leaving age, and extra energy had to be devoted to locating and distributing questionnaires to children who had left school before the sweep.

The sweep at 26 consisted of a postal questionnaire sent to the 80% of subjects for whom an address was known.

Measures available in the BCS70 cohort
(see table 5)

BCS70			
Birth	Social Class of father	Midwife interview of mother	From job description
5	Social Class of father	Health visitor interview of mother	From job description
10	Social Class of father	Parental interview	From job description
	Reading	Test at school ERT (1)	Standardised score
	Mathematics	Test at school FMT (1)	Standardised score
	Verbal & Noverbal skill	Test at school BAS (1)	Standardised score
	Handedness	Medical examination:	
		Hand used for writing (a)	R - L - Either - Cannot do
		Foot for kicking (a)	R - L - Either - Cannot do
	Laterality	Hand used for combing (o)	R - L - Both - Couldn't test
		Hand pick up ball 1st time (o)	R - L - Either - Couldn't test
		Hand pick up ball 2nd time (o)	R - L - Either - Couldn't test
		Foot for stamping (o)	R - L - Both - Couldn't test
		Hand picks up tube... (o)	R - L - Both - Couldn't test
		... to which eye? (o)	R - L - Other
		Sorting matches	2 - 500+ seconds for each hand
16	Social Class of father	Questionnaire response	From job description
	Handedness	Questionnaire response (a):	
		Hand used...	} Always R - Usually R - No pref
		... for writing	} - Usually L - Always L
	Laterality	... to throw a ball	As above
		... to hold a racquet	As above
		... to hold top of a broom	As above
		... to hold top of a shovel	As above
		... to strike a match	As above
		... to hold scissors	As above
		... to deal cards	As above
		... to hold a hammer	As above
		... to unscrew a lid	As above
26	Social Class of subject	Questionnaire response	From job description
	Number of children	Questionnaire response	
	Highest qualification	Questionnaire response	
	Age at first child	Questionnaire response	
	Gross income pre week	Questionnaire response	

Table 5. Measures used at each age from BCS70

(1) Tests of intellectual performance:

Reading: Shortened Edinburgh Reading Test (ERT) (Self- completion). The Edinburgh Reading Test is a test of word recognition and the shortened version used in this study was made up of items extracted from the full Edinburgh Reading Test after consultation with its authors (Godfrey Thomson Unit, 1978). Items were carefully selected to cover a wide age range of ability from seven to thirteen years in a form suitable to straddle the ten-year cohort. Particular attention was paid to the lower limit to allow a score to be allocated for very poor readers. The shortened test contained 67 items which examined vocabulary, syntax, sequencing, comprehension and retention.

Mathematics: Friendly Maths Test (FMT). The lack of a fully acceptable mathematics test appropriate for ten year olds led to the development of a special test for the BCS70 Ten-year Follow-up. This was done in collaboration with Colin Appleton and John Kerley, specialists in primary mathematics. It was piloted in two halves in Bristol schools each on 400 children. It consisted of a total of 72 multiple choice questions and covered in essence the rules of arithmetic, number skills, fractions, measures in a variety of forms, algebra, geometry and statistics.

Verbal & Non-verbal skill: British Ability Scales (BAS) (Self-completion). This is a test of cognitive attainment measuring something akin to IQ (Elliot et al, 1978). After consultation with the designers of the test, two verbal and two non-verbal sub-scales were selected. Verbal sub-scales comprised word definitions (37 items) and word similarities (42 items). Non-verbal sub-scales comprised recall of digits (34 items) and matrices (28 items). Administration of the test had to be adapted so that it could be done by teachers. The scoring of this and the next two tests was carried out when the completed forms were returned to Survey Headquarters.

(a), (o) Laterality measures:
(a) These are answers to questions, either verbal (from examining doctor) or on a questionnaire ie. the information is recalled by the subject.
(o) These are observed behaviour, in the context of the medical tests
- a ball was picked up on 2 occasions after being placed midway between the child's feet and 12" in front of the child
- the child was asked to mime combing their hair
- A coin was placed some distance from the child, and they were asked to stamp on it
- A rolled sheet of paper was held in both hands and offered to the child, and the child was told "Let's pretend this is a telescope. Can you show me what you do with a telescope?" (or similar phrase), and the child's actions recorded.
- The child was timed moving 20 matches from one matchbox to another with each hand in turn.

Measures used in the analysis
The strategy applied to the NCDS measures was applied again.

Attrition
Attrition has been more of a problem in BCS70 than NCDS. This is seen clearly in the sweep at 16 (table 4), the result of a prolonged teachers' strike. The sweep at 16 was therefore greatly handicapped, as was the questionnaire survey at 26, relying as it did largely on contact data from the previous sweep.

Although detailed analyses of attrition effects on many measures exist in reports on BCS70 at 10 & 16, an examination of the effects of attrition / response bias in the variables of interest seems appropriate, as with the NCDS.

	Source	Target %	Achieved %	% Bias
Male Sex	BBS	51.8	47.8	-7.8
Manual class (father) @ 0	BBS	17.2	20.1	17.1
Manual class (father) @ 5	CHES	24.8	29.6	19.4
Manual class (father) @ 10	CHES	30.2	35.8	18.3
Left handedness @ 10	CHES	11.6	11.3	-2.4
Left handedness @16	CHES	11.4	11.9	4.8

Table 6: Effects of attrition on some target variables in BCS70

Hence there is some under-representation of males in the sweep at 26, which sits well with literature on a male excess of births and excess in male mortality. Manual social class of father is markedly over-represented (in contrast to a mere 2% bias towards under-representation in the NCDS), suggesting adjustment will be needed for any findings that are associated with social class. Left-handedness shows equivocal results, under-representation of lefthandedness as recorded at 10, and over-representation of the measure recorded at 16.

Discussion

Issues of data quality
Social class as a category is a reduction of job type that has been formulated and re-formulated many times over the years. As a consequence, comparisons over time in a given cohort can be problematic, as individual jobs at the boundaries might flit between categories over time. However, for the purposes of these analyses, social class of subjects at the last sweep in each cohort is being examined, as an outcome, and no attempt has been made to quantify changes over time. Indeed, principal components analysis of social class in NCDS shows father's and subject's social class loading heavily on different factors, a reassuring notion for any determined to 'better themselves'.

After some debate, it was decided that weekly pay would be used as the measure of financial 'success'. Determining rates of pay per hour didn't seem to get to the heart of income as an indicator of social standing. While Machiavellian manipulators might be successfully earning the same wage for fewer hours, the issue seemed to come down to earning power: not what someone could achieve if they really put their mind to it, but what they actually <u>did</u> earn. Understanding net income required too many assumptions about the nature of deductions. Similarly, the notion that being self-employed indicated success was not felt to reflect the 24 hours a day, 7 days a week experience of the majority of self-employed individuals.

A lot of information exists in both cohorts to describe in detail subject's experience of education. However, as with income it was decided that maximum absolute 'level' of education best illustrated overall success in this field. While not denying the effects of deprivation on provision and uptake of education, there is no suggestion that handedness or laterality are functions of social class. Hence deprivation effects should not confound any associations between measures of handedness and educational success.

The handedness measures were a mixture of types, but were gathered according to a written rubric using standardised questioning, or testing using equipment that was readily available, and therefore uniformly provided.

Issues of data type
A wide variety of handedness and laterality data types are present. There are recalled preference items in abundance, as well as some observed preference measures. However, as these are categorised in different ways in different ages & cohorts, they will be not be analysed further (although no significant associations were found in an analysis of hand preference with respect to cognitive ability in NCDS, Whittington & Richards 1987, 1991). The variables here also illustrate that even preferred hand for writing can be conceptualised in a variety of different ways - frequency of use, preference of use, absolute observation of use etc.

For the most part, the observations are single measures in many individuals, although "hand picking up ball" is recorded on the 1^{st} and 2^{nd} occasions. Significance of these binary categorical measurements, whether statistical or operational, is unclear. Otherwise there are no repeated measures with which one could examine effects of 'learning' or 'fatigue' on RL differences.

In the NCDS we have measures of hand, foot and eye preference at 7 and 11, but they are recorded as trinary (right, left or mixed) at age 7 and binary (right or left) at 11. It is therefore not possible to use them to observe changes over time in the measures themselves as they are conceptualised quite differently at the two time points. Examining the measures in BCS70, we can see that the only measure repeated over time is hand used for writing, and even this requires an assumption be made about how subjects would code their 'Usually R (or L)' responses.

It is frustrating that the lack of continuity of measures between sweeps of both of these cohorts mean no examination of hand skill over time can be made. The best that can be achieved is a comparison of associations with match-picking skill between the cohorts, as the tests in each cohort are at very similar ages, and the two tests are all but identical.

Analysis will therefore be restricted to the tests of hand skill and recalled writing hand preference at the time of these tests.

Finally, the cohorts represent different epochs, and are going to be used to compare any findings, as a test of any hypotheses. Given the suggestion of the profound neuropsychological differences represented by differences in handedness, it is not anticipated that any relationships observed will be substantially different in each cohort.

Chapter summary

The utility of birth cohort data in considering the thesis is discussed. The chief benefits for this thesis are the large numbers of cases with systematically-collected data, without the confounds of different age or social class bias.

Two of the three UK national birth cohorts are described, the effects of attrition on their data examined, and the nature and origin of the measures of interest are described.

Despite a large number of measures of handedness, 'laterality' and hand skill being recorded, writing hand preference and measures of hand skill are used to form the focus of further analysis, in order to maximise the reliability, validity and consistency of comparisons between the cohorts.

Chapter 6: The NCDS & BCS70 psychiatric casefinding

Introduction

The final outcomes considered in this thesis, and examined in relation to measures of handedness, are those of psychological function as reflected by the admission to a psychiatric inpatient unit. This chapter contains
- a discussion of the utility of examining such outcomes in cohort study data, and
- a detailed description of the process of casefinding this author undertook.

Why identify birth cohort members in psychiatric admissions data?

The aetiology of psychiatric illnesses has often been related to both birth trauma and abnormalities of development. For example the organic changes noted in schizophrenia (eg. Johnstone et al. 1976) have been related to birth trauma (eg. Reveley 1980; Wrede et al. 1980) and anomalies of physical development (Guy et al. 1983). Poor premorbid status both educationally and socially has also been reported in schizophrenia although their onset and course is poorly documented. Similarly endogenous depression is thought to have an organic basis possibly related to obstetric complications and secondary depression is a sequel to pertinent life events (eg. Robins et al. 1972).

Complete obstetric and developmental histories are rarely available. Most of this kind of data is usually collected retrospectively and as such is prone to incomplete retrieval of details and sampling error leading to both Type I and Type II errors. The collection of prospective data obviates such problems. The initial phase of this research project was designed to gain a better understanding of the early determinants of psychiatric illnesses by utilising the wealth of data in the National Child Development Study (NCDS) database.

Identifying cohort members who suffered from mental illnesses as adults would provide a dataset on patients selected only by their inpatient status, along with a 'whole population sample' of controls, the data gathered systematically and prospectively over several decades. Such data could be used to plot the developmental trajectories of individuals and groups into illness, compared to those who may share the risk factors but not become ill.

Initially an attempt was made in the early 1980's to identify cases with psychiatric histories from the NCDS database itself, since it contains questions relevant to this. This identified a number of cases who have suffered from transient disorders, but only one case of definite schizophrenia. It was noted that there had been an attrition of some 25% of the original sample and it is well known that psychotics drift from address to address, although they are usually admitted at least once to a hospital. It seemed likely therefore that the NCDS database would be biased. Indeed, an earlier study (MRC National Survey of Health and Development (NSHD)) based along similar lines obtained only one case of schizophrenia via their interview technique, but subsequent analysis of in-patient records using the Mental Health Enquiry (MHE) database revealed another 21 cases.

The advantage of a study focussing on schizophrenia is that about 80% of episodes are admitted during the first episode (Ødegaard 1952). Consequently, looking at data on hospital admissions would not only uncover probable birth cohort members (by a search for appropriate dates of birth), but would also pick up the majority of cases of schizophrenia, even if this were the only episode. For other illnesses, cases will be skewed towards the more severe end of the spectrum. For example, only 50% of cases of bipolar psychosis (still a very severe mental illness) were admitted in the above series.

The original 'follow-back' trace: NCDS in 1985

At one time MHE data, on hospital admissions 1974-1986, were centralised, but since the introduction of the Data Protection Act subject identifiers were removed. Such data became only accessible in MHE data kept by Regional Health Authorities.

Approval was sought from the fifteen regional health authorities, two special health authorities and four special hospitals, and once obtained regional statisticians screened MHE data tapes for any psychiatric admissions with a DOB of 3-9/3/1958. 698 admissions were identified in this way.

The then MRC Senior Research Officer, Dr DJ Done, was sent details of each identified case (ie. hospital number, DOB, dates of admissions, and hospitals of admissions). After accounting for readmissions, 698 admissions originally identified were found to represent 252 individual cases. Between 1985-7 he contacted the consultant psychiatrists responsible for each, giving details of the research project and asking if they were willing to disclose the identities and reveal psychiatric histories to him.
In 4 cases the consultant refused permission
In 13 cases the notes were irretrievably lost.
In 235 cases the consultant psychiatrist sent DJ Done case notes, or occasionally photocopies, from which Dr EC Johnstone filled in PSE forms from which CATEGO diagnoses were obtained.

Results

The results of this exercise were the identification within the NCDS cohort of:
49 individuals with narrow schizophrenia (PSE S+/S?)
79 individuals with broad schizophrenia (PSE S+/S?, P+/P? and O+/O?)
44 individuals with affective psychosis (M+/M?, D+/D?, R+/R?) and
93 individuals with neurosis (N+/N?).

Several influential publications have resulted from analysis of this data (Done et al 1991, Done et al 1994, Crow & Done 1992).

It will be noted that the number of cases appears relatively small compared to the base population. However, the numbers are actually remarkably representative: if schizophrenia has a lifetime prevalence of 0.8-1%, a group of individuals aged 27 will have 'used up' 36% of their lifetime risk (Gottesman 1991). Extrapolating from 16,457 individuals in the cohort at 23, in a cohort of 16,000 individuals aged 27 gives an 'expected' range of 46-58 individuals with schizophrenia.

However, when multiple births, immigrants and otherwise unusable cases not present in the cohort were excluded, the number of cases of narrow schizophrenia dropped to 35, and some subsequent analyses using measures from later sweeps of the cohort have had even fewer cases available with data at the required ages. As a consequence, sex-differences have proved ill-defined, and null results from this otherwise well-validated and authoritative dataset are less than definitive. It was therefore decided in the early 90's to repeat the exercise, to include both cases incident in past decade, and also to identify individuals in a second of the three UK national birth cohorts, the 1970 British Births cohort (BCS70).

The repeat trace: NCDS in 1995, and introducing BCS70

Methods

The NCDS database has been widely used for medical research purposes. It has its origins in the Perinatal Mortality Study (PMS) in which an attempt was made to monitor the social and obstetric factors of all births in mainland UK during the week 3rd-9th March 1958. 98% of births in that week (17,414) were included in the cohort, as well as 7,000 stillbirths and neonatal deaths occurring over a three-month period. This database formed the basis of the National Child Development Study (NCDS), which has subsequently been followed up at ages 7, 11, 16, and 23 at which times information was obtained from teachers, school health services as well as the subjects themselves. The target sample was subsequently augmented by immigrants born in the relevant week, that were picked up in sweeps at ages 7, 11 and 16.

BCS70 is a relatively under-exploited cohort database, consisting of 17,196 births recorded between the 5th-11th April 1970. A sub-sample was followed up at 22 months, and the entire cohort has been followed up at the ages of 5, 10, 16, and a subset at 26. Information was gained from obstetric notes, maternal interviews, and direct testing/questioning of the individuals themselves, on a wide variety of social, behavioural and performance measures.

The Körner dataset replaced the Mental Health Enquiry (and several other data-collection instruments) in 1987, as an attempt to standardise a dataset that would comprehensively describe activity within the whole of the National Health Service. It too contained information regarding psychiatric admissions. However, with the reorganisations within the NHS in the early 1990's, regional databases were being transferred from the (closing down) Regional Health Authorities to private-sector data management companies. It was therefore in a context of great change that this expanded case-finding exercise was undertaken.

Support for the project was obtained from Regional Ethical Committees, although the re-ordering of health service administration to individual Healthcare Trusts similarly complicated this process. In some instances ethical approval for the study had to be sought at a local level, trust by trust, with some disagreement at a local level as to the jurisdiction of a regional ethical committee over activities in a newly-formed trust. However, in many places senior staff who were involved in the 1985-6 exercise clearly supported this repeat exercise, and their support was greatly appreciated at this and later stages of the project. A letter of support for the project from the then president of the Royal College of Psychiatrists was obtained, and circulated as part of any discussion of the legitimacy of the project.

Data collection

A number of different approaches were taken by different regions, but there was overall consensus that disclosure of patient information should be at the discretion of each individual's RMO.

1. Region released lists of patient admissions & consultant identifiers
In response to differing conditions imposed by different ethics committees and different data formats, admissions data were made available in a number of ways. In some regions (Northern, South Thames, Wessex), admissions data were released to us directly, and consultant by consultant requests were made for permission to access the notes. Whether or not the patients were asked individually for consent was left to the consultants (see discussion).

2. Region released lists of patient admissions only

In some regions (East Anglia, Mersey, North Western, North West Thames, Scotland, South Western, Trent, West Midlands, Yorkshire), data contained no consultant identifiers, in which case the first request was to local records officers, to determine the relevant RMO. Where this proved impossible, a request was made to the local clinical director, for a decision, usually after discussion with the local medical committee.

Patient identifier codes: In only one region was a list of admissions with patient names released to us; in all others, patients were referred to by a combination of date of birth (not very discriminating in this context), dates of admission, sometimes unit admitted to, and in most cases an ID number.

Patient identification numbers sometimes referred to local hospital ID's, sometimes to regionally-held identifiers that were not part of a local hospital's database. There was seldom consensus as to how these numbers ended up on regional admissions database. Local records officers in many regions diligently sought to interpret these numbers, and if this was possible, cross-checking of a correct 'translation' was possible with the date of birth, and dates of admission.

At this point it was possible to determine the RMO, or the RMO now responsible for that patient or sector if the original RMO had moved on. Records officers demonstrated a great deal of enthusiasm and ingenuity, but were often working with information systems that could not, for example, cross-reference patient's dates of births with consultant names or dates of admission.

Where the patient identifier was un-interpretable and no RMO information was given, the trail often went cold. Asking local records offices to search for psychiatric admissions with appropriate dates of birth was not only felt to lie beyond the remit allowed in ethical clearance, but also proved to lie beyond the technical capability of most records offices involved.

3. No patient identifiers released until after consent from RMO

In some regions (Anglia and Oxford, South West Thames, Wales), it was felt that we should not be allowed sight of any patient identifiers at all until consent had been obtained from the RMO. In these cases, consultant names were released to us, and they were asked whether they would consider assisting the study. If they did, they had the choice of being supplied with identifiers of the patients concerned directly by the regional databases, or via this study. Several admissions were 'lost' to the study in these regions due to the difficulty of chasing responses when it was unclear when and to whom information had been sent. The success of the project in these regions is a testament to an impressive level of commitment of the regional database managers over a considerable period of time.

There were subtle differences in the nature of the population identified by the regional statisticians; although most region's data identified psychiatric admissions, some regions eg. Wales seemed to gather a broader range of admission data, resulting in casenotes of some individuals that only seem to have been seen in casualty, or admitted overnight with a head injury. This added redundancy in the process of casefinding could of course also be the result of mis-identification of the notes this study was requesting.

4. No notes, but OPCRIT forms filled in
In some instances where consultants were unwilling to release casenotes, they did complete OPCRIT questionnaires. The option of releasing anonymised information to the study, with the patient identifier under sealed cover for the eyes of the cohort dataset managers only, was taken up in one instance only.

5. No direct contact with us, the researchers, at all
The option of communicating directly with the cohort dataset managers, for 'complete anonymity', was not taken up.

6. No regional listing made available.
In the case of Special hospitals (eg. Broadmoor, Ashworth) and the North East Thames region, no centrally-held list of patient admissions was obtained. The Special Hospitals were not included in regional listings, and North East Thames record-keeping had been privatised, and quoted a five-figure sum for processing their records to obtain the necessary data. In these cases, permission and casenotes were sought on a trust-by-trust basis. The response from several trusts in North East Thames was a statement that "There are no patients with these dates of birth on our records"; the overall number of casenotes eventually obtained from this region were small.

Method of casenote analysis

OPCRIT diagnoses
Casenotes were examined with regard to three broad outcomes. First, it was noted what working diagnosis/ diagnoses had been arrived at by the clinicians treating the patient at the time. Second, the notes were examined using OPCRIT (Craddock et al 1996). This computerised multi-classification system was developed for use in collaborative studies of psychosis, and consists of 90 questions to be answered from the clinical information available, which are then computer-analysed in a hierarchical fashion to derive diagnoses according to the major classifications (DSMIII-R, ICD10, RDC etc.).

DSMIV diagnoses
Finally, SL and MB independently examined the casenotes to derive axis I and axis II disorders according to DSMIV criteria. After an initial analysis of inter-rater agreement, discrepancies were resolved in discussion between SL, MB and TC.

Identifying patients in the cohort dataset
Using names and demographic data in the casenotes, individuals were identified as cohort-members in an exercise carried out and overseen by Dr Peter Shepherd, manager of cohort information at City University in London.

Results

868 admission episodes were identified in total from all sources. These reduced to

467 individuals, documented in 551 individual sets of casenotes (470 received), photocopies of casenotes (77) and 8 OPCRIT ratings performed by the consultants themselves.

3-9th March 1958:
302 episodes relating to 219 individuals identified last time, 182 (83%) of which were eventually identified as cohort members.
270 episodes relating to 122 individuals not identified last time, 83 (68%) of which were eventually identified as cohort members.

5th-11th April 1970:
180 episodes relating to 125 individuals, 91 (73%) of which were eventually identified as cohort members.

(92 related to patients in the National Survey of Health and Development, whose identifiers were originally sought from regions when the scope of the study was hoped to include them. This arm of the study was dropped early on when it became clear that access to the cohort data would be problematic)

1 under separate cover - eventually not identifiable in cohort records.
23 cases were never identified, as the process of obtaining consultant permission to access the identifiers was unsuccessful.

The remaining 333 episodes are accounted for as follows:

206 episodes (representing 125 individuals) were found to refer to individuals on whom notes had already been obtained. In some cases this was discovered only when casenotes arrived with psychiatric notes that were duplicates of those obtained from elsewhere arrived; in others, sufficient information was available at an earlier stage to discover this (in discussion with local records officers).

24 sets of notes were identifiable in local records but in practice unobtainable ie. there were records of the notes existence, but it proved impossible to track down the notes themselves. In one case, this was attributed to a fire in the department some years before.

28 episodes were unidentifiable from the patient ID code made available. It was suggested this was due to there being different regional and local patient ID numbers. The regional databases held no further information.

30 were 'not known' despite the availability of further identifying information eg. name of patient and or name of consultant.

23 cases were never identified, as the process of obtaining consultant permission to access the identifiers was unsuccessful (largely as a result of the named RMO having moved elsewhere since the admission).

5 episodes remained unidentified after consultants failed to obtain consent.

4 episodes resulted in patients explicitly refusing consent (unfortunately, data were not available on the number of consultants who successfully obtained consent).

4 episodes were lost after two consultants refused to take part in the study. One stated clearly that his concerns were over confidentiality, and neither responded to further correspondence.

2 consultants stated they were too busy to take part in the study (one of whom had asked to OPCRIT the notes themselves).

2 episodes were identifiable locally, but it did not prove possible to identify a RMO, or a body in a position to make a decision regarding the study.

1 under separate cover - eventually not identifiable in cohort records.

(Total = 401)

Thus, attrition through lost notes and un-interpretable identifiers (82 episodes) far exceeded any problems with releasing data (41 episodes). Casenotes were sent in the vast majority of cases, although some photocopied sets of casenotes were sent.

Diagnoses:

OPCRIT RDC diagnosis	Old NCDS	New NCDS	BCS70
'None'	110	49	52
Major depression	30	34	17
Mania	2	1	0
Bipolar disorder	2	1	1
Schizo-affective/manic	13	2	4
Schizo-affective/depressive	11	10	10
Schizo-affective/bipolar	5	4	1
Broad schizophrenia	2	4	8
Narrow schizophrenia	34	9	16
Unspecified functional psychosis	17	7	14
TOTAL	226	121	123

Table 1: OPCRIT RDC diagnostic output: Casenote analysis

OPCRIT is designed for use in studies of psychosis. Consequently its output tends to concentrate on these diagnoses. Compared to the 35 usable cases identified in the earlier exercise with PSE Narrow Schizophrenia (Catego S+), while this process was unable to obtain the casenotes of one of these it identified a further 9 RDC Narrow Schizophrenia cases, a 25% increase in cases in the NCDS.

This somewhat disappointing figure was felt to reflect the tendency for OPCRIT, when faced with a wide variety of information gathered from numerous observers over several episodes of differing illnesses, to assign the tag "Unspecified functional psychosis" ie. the algorithm was unable to resolve conflicting clinical pictures on different occasions into a single diagnosis.

The results can therefore be compared with those obtained from the independent assessment of the casenotes by SL and MB, which aimed to provide single 'lifetime ever' DSMIV diagnoses.

DSMIV diagnosis	Old NCDS	New NCDS	BCS70
Schizophrenia	45	20	27
Schizo-affective disorder	5	0	0
Bipolar psychosis	11	2	1
Bipolar - not psychotic	3	2	2
Major depression with psychosis	3	3	5
Major depression	10	5	1

Table 2: DSMIV Casenote analysis results

Discussion

A decade on

When this exercise was performed in the early 1980's, DJD noted a clear unity of purpose between the researchers at the MRC and regional statisticians. Data were screened and made available free of charge. There was an understanding of the need for basic descriptions of these incapacitating illnesses, and the sense in capitalising on the enormously costly, largely publicly-funded effort that gathered the cohort data in the first place.

By the early 1990's, the climate had clearly changed. Disappearing health region databases supplied data, individual regional statisticians were no less interested and committed. However, the introduction of an internal market had clearly put this spirit of collaboration, between departments managing data collection, and those seeking to answer 'blue sky' questions, at risk. In the region where data management had been privatised, access to the admissions data would have required a five-figure sum, beyond the means of a project such as this, so that admissions data had to be sought on a trust by trust basis in this region. The results of trust-by-trust requests were disappointing in terms of new cases located, illustrating the utility of the old regional databases.

Cohort studies and consent

The ethical position of a national study of this sort is, and in a free society should remain, open to debate. Inclusion in the cohorts was originally through consent of the parents of the cohort members, but subsequent sweeps had been carried out with consent of the individual cohort members. However, the priority imposed by the cohort database management was for this study to avoid, if at all possible, direct involvement of the patients, as repeated requests for consent to take part in studies is a common reason for individuals' dropping out of cohort follow-up. This position had to be balanced against issues of informed consent.

In defence of not informing the patient was the fact that an individual being identified soley by their NCDS or BCS70 ID number would effectively anonymise the final dataset. Keys to these are only held by the bodies managing the cohorts, and are not available to researchers. In an attempt to maximise the anonymity, the study database was held on a single non-networked laptop computer, and this and all paperwork was kept in a locked filing cabinet, accessible only to TC, DJD and SL. The casenotes themselves were only be accessed by a single registered practitioner, SL, and the casenotes rated by two registered medical practitioners, SL and MB.

MRC guidelines are clear that "…transfer of information from medical records for the purpose of research requires the consent of the medical custodian." However, it concludes that in certain circumstances "…subject to scrupulous safeguards about confidentiality, information about patients can properly be available for medical research without their explicit consent…", and it was felt that this project constituted these special circumstances (see Appendix D). The final decision was left to the individual consultants concerned.

The cohort members identified

As was mentioned in the introduction, it is only for cases of schizophrenia that one can claim any findings from this approach generalise to the general population. Even in cases of affective psychosis, less than 50% of cases are admitted to psychiatric hospital (see above). The proportions for other diagnoses are clearly smaller still, with admission criteria playing an increasing rôle in determining inclusion in this study. These criteria are a heterogeneous group of judgements eg. 'severity', 'risk to self or others', 'treatment-resistance', and all the other reasons a patient with any given problem may be admitted to a psychiatric hospital.

The attrition of the sample at the stage of identification within the cohort databases deserves comment. Once one is attempting to locate an individual within a given cohort, their date of birth ceases to be very discriminating. Invariably, one was left with the name, and a few details such as place of birth. If an individual had changed their name the trail went cold, although occasionally the maiden-name could be identified by GPs (located by correspondence to GPs in the notes, and the FHSA central records). Frustratingly, neither NHS number nor national insurance number appeared in any but a handful of notes, nor was it recorded elsewhere in medical records departments.

It is unsatisfactory that the diagnostic criteria used previously differ from those current. The most valid comparison regarding 'percentage increase in cases' is to look at the percentage of NCDS cases obtained last time who now have a diagnosis of schizophrenia, and compare that with the total number obtained this time. It is noted that even here, some of the casenotes obtained last time were unavailable or lost this time.

Success in picking up new cases?

The cases identified in BCS70 will of course provide a unique opportunity to explore questions already addressed in the other UK birth cohorts, for example exploring relations between obstetric complications or school performance and adult psychotic illness.

Compared to the 35 usable cases identified in the earlier exercise with PSE 'narrow schizophrenia' (Catego S+), this process was unable to obtain the casenotes of one of these, but identified a further 9 RDC Narrow Schizophrenia cases, a 26% increase in cases in the NCDS. This somewhat disappointing figure was felt to reflect the tendency for OPCRIT, when faced with a wide variety of information gathered from numerous observers over several episodes of differing illnesses, to assign the tag "Unspecified Functional Psychosis" ie. the program, understandably, was unable to resolve conflicting clinical opinions on the best diagnosis to sum up a variety of differing clinical pictures. The individual independent assessment of the casenotes by SL and MB, with a view to providing DSMIV diagnoses, was hoped to be a satisfactory method of resolving this.

Of the 35 useable S+ individuals identified last time, 32 were assigned DSMIV diagnoses of schizophrenia. Direct comparisons of total numbers are difficult, as different raters were rating different material. However, it is possible to use items from the OPCRIT questionnaire to 'construct' a measure that contains the same components as PSE S+. This provides one with 35 old 'S+' cases (!), 10 new 'S+' cases, and 17 'S+' cases in BCS70.

Hence the sample size in the NCDS may be seen to have increased by 10 (29%) in terms of useable S+ cases, or from 45 to 65 cases of DSMIV schizophrenia - an increase in sample size of 45%. This latter figure is hoped to be sufficient to allow for the investigation of sex differences in this condition whose relative rarity has thus far confounded attempts to analyse these in birth cohorts.

Target versus achieved population
As with the previous sweep, we can make a prediction about the number of cases we 'could' have picked up in each cohort.

NCDS:
Admissions data up to 1994-5 is about a target population that is about 37 years old. If schizophrenia has a lifetime prevalence of 0.8-1%, a group of individuals aged 37 will have 'used up' ~68% of their lifetime risk (Gottesman 1991). Extrapolating from 16,455 individuals in the cohort at 33 (Ferri 1993), in a cohort of 16,000 individuals aged 37 gives an 'expected' range of 87-109 individuals with schizophrenia.
The optimistic estimate is therefore that 80% of cases of schizophrenia were picked up (70 DSMIV schizophrenia/schizoaffective).

BCS70:
Admissions data up to 1994-5 is about a target population that is about 25 years old. If schizophrenia has a lifetime prevalence of 0.8-1%, a group of individuals aged 25 will have 'used up' ~36% of their lifetime risk (Gottesman 1991). Extrapolating from 13,500 individuals in the cohort at 26 (Despotidou 1997), in a cohort of 13,000 individuals aged 26 gives an 'expected' range of 37-47 individuals with schizophrenia. The optimistic estimate is therefore that 73% of cases of schizophrenia in the cohort were picked up (27 DSMIV schizophrenia).

Both of these estimates suggest this casenote finding exercise has identified most of the 80% of cases that Ødergaard suggests will be admitted to hospital (the other 20% probably represent less severe, or more insidious-onset cases).

Cases missed?
Let us briefly consider the possibility that cases have been missed. The impact of the missing cases on subsequent analyses depends mainly on whether they inject any bias into the cases.

On the one hand:
1. Regional admission listings were blind to diagnosis.
2. Casenote requests were blind to diagnosis.

On the other:
3. Casenote availability: Schizophrenic illnesses are often accompanied by extensive dog-eared casenotes, and the more notes are used, the greater the chances that they'll be mislaid. Schizophrenia might therefore be over-represented in the 24 casenotes that could not be located.
4. Casenote release: The decision to release notes was in the gift of individual psychiatrists, which may have introduced bias. All that can be said about the patients whose notes were withheld on the basis that the patients refused permission is that their diagnosis are unknown. The small number of patients per consultant (median = 2), and the small number of casenotes refused (11) meant an analysis for 'differential release of non-psychotic notes' was not possible. Even if all 11 cases lost to consultant refusal (consultant or patient) were schizophrenia these would not make up numbers.

Effects of the 'missing cases' on subsequent analyses
The 'missing cases' will lead to a decrease in power through reducing the number of cases, increasing the risk of a type II error. However, missing cases are very unlikely to have much effect through 'dilution' - increasing rates of important exposures in the control population - as the numbers are tiny in comparison to the control population. Any effects we're likely to observe are small compared to the difference in sizes of our case & control population.

For example, if the control group were only twice the size of the case group, and the odds ratio for a given exposure were 2, placing 25% of the cases into the control group will only alter the odds ratio by about 10% (see below). As the relative size of the control group grows, so the change in odds ratio will decrease.

All cases identified:

	Not exposed	Exposed	
Controls	100	100	
Cases	33	66	odds ratio =2

Place 25% of cases into the control group:

Control	108	116	
Case	25	50	odds ratio = 2.1

(assuming failure to identify a case is independent of exposure)

Table 3: The effect on odds ratio of missed cases being treated as controls.

Thus the number of cases identified lies close to the numbers that might be expected. Any missing cases will be unlikely to bias any findings. Least severe cases will be under-represented, but if there is a dose-response relationship between exposure and outcome ie. odds ratios for less severe cases are smaller, from the above example it is clear that any effects of dilution will be smaller still.

Conclusions

The UK national birth cohorts represent enormous expenditure and effort over many decades, and constitute a unique opportunity to examine the development of a wide variety of conditions in a whole population over time. The commitment to anonymity by the managers of these cohorts has not only ensured their enduring membership and quality, but also provides a sound basis for national 'follow-back' studies of this kind. That this resource should be utilised in this highly cost-effective fashion, directed at examining the development of psychiatric illnesses in general and psychotic illness in particular, seems a satisfactory approach in the absence of a national case register.

The introduction of national health information systems would of course make such an exercise relatively straightforward, improving as it would accessibility of information. This would only be true prospectively, however, as the task of entering data retrospectively is beyond the scope of any data service proposed thus far.

The issue of consent would, and perhaps should, remain thorny. It seems appropriate that individual RMOs be allowed their own mind regarding disclosure of a given individual's notes to a given study, and the need for that individual's consent, as an essential part of the doctor-patient relationship. It is difficult to imagine what body could or should supercede this function, even in the interests of making epidemiological research into unsolved health problems easier. Recent events in Iceland, where a private company has bought a national case register, suggest that involvement of the free market is not obviously going to make ethical considerations any easier. As information systems are developed, facilitating research of this sort, so the intrusion of market forces into the structure of the National Health Service may make the sort of cross-profession collaboration necessary to make such projects work increasingly expensive, as was apparent during this study.

Whether an exercise such as this could be repeated is questionable. If the technical and ethical issues can be resolved, it should, both to increase the number of cases and statistical power, and to continue to use the UK national birth cohorts to provide complete descriptions of how these significant conditions develop over a lifetime. Such information will not only contribute to our understanding of the natural history of the conditions, but also continue to provide valuable clues as to their aetiology.

Finally, it should be remembered that this exercise succeeded in identifying cohort members whose mental disorder had resulted in an inpatient episode. As was noted earlier, although this will result in the identification of around 80% of cases with schizophrenia, it will be identifying much smaller proportions of other illnesses, and these will be those individuals whose qualities make admission more likely, rather than simple issues of severity. Differences in local practice, expectation and service provision, risk assessment, and numerous individual factors will all come into play in selecting other which of the other diagnostic groups are recorded here.

Thus, despite difficulties in identifying some of the patients in the cohort database, this casefinding excercise yielded the numbers of cases of schizophrenia that might have been expected given the population size, age, and Odegaard's estimate of admission rates for schizophrenia. The numbers are satisfactory for the main aim of this study, which was to obtain cases for simple by-sex comparisons of means. Unfortunately this number is far from ideal for the technique of presentation of laterality data eventually employed in Chapter 9, which is suited for hundreds to thousands of cases, not tens. However, sometimes it is perhaps preferable to use the best cases rather than the most numerous. Given that this represents in many ways the most methodologically sound sample of such cases obtained in the 20th century, it seemed reasonable to use them in what would at least be a tentative examination of laterality in psychosis, in comparison with the population.

Chapter summary

Between 1995-1996, casenote diagnoses were obtained on members of two UK national birth cohorts admitted to psychiatric hospitals. A similar process had been undertaken in 1985 for one of the cohorts (NCDS). This repeat was attempted to increase the numbers in this cohort and to include a further cohort (BCS70).

After obtaining ethical clearance on a region by region basis, Körner data held by rapidly-disbanding health regions was screened for individuals admitted to psychiatric hospitals with relevant dates of birth. Casenotes were obtained where available, and these were examined in order to determine standardised diagnoses. In total, data on 868 admission episodes was obtained, resulting in 467 individuals being identified from 551 casenotes obtained. 76% of these were identified as being members of the two birth cohorts under investigation. This exercise resulted in a 45% increase in cases of schizophrenia from those obtained in 1985. The numbers of cases fall close to those that might be expected if admission casenote finding were complete, and any missed cases will only increase the risk of type II error.

Chapter 7: Associations between lateralization and function in the cohort data

'Hemispheric indecision'

A relationship between handedness and ability at last?

Introduction

The question of whether lefthandeders are cognitively disadvantaged in some way has a long history. Certainly a 9:1 R:L population bias brings with it biases against lefthandedness via sociological mechanisms (eg. the 'herd mentality'), and research into handedness and performance has undoubtedly arisen out of attempts to justify the prejudice against it. More recently the question has been framed in genetic terms, eg. 'Is lefthandedness bad for you?' (see chapter 3). For the genetic theories one has to propose either a balanced polymorphism or a gene for a 'primary' phenotype that is linked to handedness. A simple 'gene for lefthandedness' would be selected out fairly rapidly even given a fairly small performance disadvantage (Dawkins 1999).

However, the most striking finding has been that, despite the best efforts of numerous researchers, right and left-handers perform equally well in all areas, apart from the inevitable hail of small effects of dubious significance found around most null findings (see chapter 3). In this and other ways the argument shares similarities with genetic theories of psychosis; you wish to explain fixed prevalence, stable over culture and geography, and findings relating it to cerebral asymmetry. Amidst such stability, associations with variability are elusive.

This thesis suggests that a failure to characterise a relationship between handedness and other measures of brain function, including hand performance, is a type II error due to the problems enumerated in chapters 1 & 2, and not because there is nothing going on. For example, while keeping hold of the significance of the 9:1 R:L population bias in writing hand, it seems that formulating quantitative investigations in terms of 'writing hand preference' has not yielded much. The categorical measure is either too broad or too noisy. Examination of alternative conceptualisations of the phenomenon eg. performance measures may yield something of interest. Then, if there is a relationship, this will be clearer if one avoids making too many assumptions about the distribution of the data, and the confounding inherent in laterality indices. One could even avoid laterality indices altogether.

This chapter describes two studies exploring evidence in cohort data for a relationship between relative hand skill and academic ability. Relative hand skill is seen as a proxy measure of lateralization of cerebral function. The connection can be inferred by the association, albeit imperfect, between hand preference and side for speech dominance. It is not assumed that ‘side for speech dominance’ is all, only that both concepts may reflect an underlying factor that is species-specific and accounts for the population hand preference bias and generative language unique to mankind. Occam's razor is thus invoked, in the absence of competing hypotheses, although the findings could be seen as supporting other hypotheses (eg. Annett's heterozygote advantage).

We shall examine the relevant sections of these two papers. They succeed in disclosing a relationship between measures of functional asymmetry and cognitive function.

PAPER 1: "RELATIVE HAND SKILL PREDICTS ACADEMIC ABILITY: GLOBAL DEFICITS AT THE POINT OF HEMISPHERIC INDECISION" Crow, Crow, Done & Leask 1998

Introduction

This study arose from the suggestion that the persistence of population variation in handedness, the latter a correlate of cerebral dominance for language, could reflect a balanced polymorphism with respect to cognitive ability. The aim was to examine cerebral function with respect to a measure of handedness.

To recap, the Crow hypothesis is that 'generative language' has evolved in Homo sapiens as a consequence of increased cerebral lateralization (Crow 2000). As with malaria and sickle-cell disease, however, the advantage comes with a price in a proportion of individuals. The language gene leads to 1% of the population developing psychosis, a condition the core of which is a breakdown of the central engine of language.

It then follows that, if selection is still in force, one may observe genetic variation for other aspects of cerebral function. Asymmetry between bilateral structures (or functions) can be conceptualised as a continuous measure varying between individuals for a given task. Attempts to expose differences in cerebral performance by dichotomised writing hand have failed. The Crow theory might predict that cerebral performance will fall near zero values of an index of lateralization of cerebral function ie. there will be evidence that a bit of lateralization of function is good for you.

Methods

Data from the NCDS was used. The verbal & non-verbal parts of the General Ability Test, Reading Comprehension and Mathematics at 11 were used, along with performance by hand at the box-ticking task, and the response of carers to 'Hand used for writing?' (ie. observed writing hand, not recalled).

Main findings

Four main findings were demonstrated in this paper
1. A histogram of standardised box-ticking performance index is a bimodal curve, with the appearance of two normal plots placed roughly equally either side of and overlapping about the x-axis zero.
2. Dividing subjects into two groups by writing hand results in two near-normal distributions.
3. Plotting mean verbal ability on the y-axis and decile bins of laterality index on x, for laterality index nearest to zero there is a significant deterioration in cognitive function.
4. Dividing the groups by writing hand and using locally-smoothed plots demonstrates that this dip around zero is due to a fall-off of verbal skill towards <u>and beyond</u> zero, by writing hand. Female superiority on the verbal tests is also demonstrated clearly.

5. Female superiority was clearly demonstrated in the verbal task.

Comments
1 & 2. This has been noted before, in this same data, by McManus (1985). He suggests that the distribution is a mixture of two normal distributions, and further, that there are therefore just two types of handedness, left and right; all the variability in performance is just fluctuating asymmetry and/or measurement inaccuracies.

3a. The dip around zero is not obviously a prediction of previous theories, although the association of mixed-handedness preference with poor verbal skill was noted by Annett back in 1970. In her sample of schoolchildren of a variety of ages, it was noted that the lower mean around zero was accompanied by an increased variance ie. near zero there was a greater concentration of poor verbal performers. This was echoed in the key critique of this finding by McManus, an original referee to the paper: Many forms of mental handicap are associated with decreased right-left skill difference (McManus et al 1992, Cornish, Pigram & Shaw 1997), and as such these handicapped individuals could account for the drop in the mean.

In this data, removing individuals identified as handicapped in the cohort did not remove the central dip. However, in the cohort data there is under-reporting of cases, especially the less-severe. Crow et al. also looked at this by removing the bottom 10% of verbal scores. Removing these (arbitrarily-defined) low-performers did not remove the effect either. However, in pursuing this exercise, adjusting the cut-off, an ugly truth emerges: if you define poor performers as measured in the tests, and then remove these from the dataset, you are completely at the mercy of your (arbitrary) poor-performance cutoff and the variance in the data. Inevitably, such a manipulation skews the plot:
- upwards where there were a lot of low values, and
- less upwards where there were mainly high values!

The manipulation is potentially artefactual, and does not therefore shed further light on the McManus critique.

Ultimately, whether handicapped individuals are secondarily more functionally symmetrical, or whether functional symmetricality is of itself a handicap, can become a circular argument outside the confines of clearly-defined 'pathologically handicapped' groups. That individuals around zero are in some general way handicapped is not under dispute; indeed, one could speculate that the unknown mechanisms leading to many forms of mental handicap share a lack of fully-developed brain asymmetry.

3b. This is a good example of a confusing figure. The notion of central symmetry leading to a handicap is not well served by a figure in which the central 'bin' is way over on the left.

Further, bins of data keep the confidence estimates confusing. More bins will increase your 'resolution' on the x-axis, but there are fewer cases in each so the confidence limits get larger, making effects non-significant. Fewer bins could risk missing the effect around zero altogether.

4a. At the outer extremes, performance also seems to decrease somewhat, which could be taken as evidence of the 'heterozygote advantage' predicted in Annett's right-shift theory. In the Annett theory, degree of right-advantage is at least partially genetically-determined, and extremes of right-handedness should be characterised by less-than-optimal performance, to provide pressure to maintain a balanced polymorphism. Sadly, the right-shift theory does not predict any parameters of disadvantage by which we may test how well this data fits the prediction.

As with the histograms, preferred writing-hand can account for an important proportion of the variance in RL difference. If the grouping were spurious, performance should pick up either side of zero, for a given group. Instead, it continues to deteriorate on the non-preferred side. The validity of grouping by writing-hand remains contentious. In the absence of an over-arching theoretical model of how the preference arose, it could still be maintained here as a species-specific behavioural marker.

4b. The local-smoothing approach results in figures that are much more readily-appreciated, with zero laterality in the centre, and clear presentation of eg. sex differences. The computer package SPSS for Windows did not provide any estimates of the error in the smooths. However, significance of the findings could be appreciated in terms of the consistency of the trends between cognitive tests, and the error bars from the by-bin analysis.

5. The magnitude of the female verbal superiority was greater nearer the population mean of laterality than near zero. Further, the female population mean of laterality was greater than the male mean. This suggests the verbal sex difference may also be a function of degree of lateralization. This finding was felt to support the notion of a degree of sex-linkage in the genetics of cognitive ability and lateralization, which had been suggested elsewhere (Corballis 1996, Goodman 1997).

Discussion

There are two obvious critiques of generalisation from these findings. The first is that box-marking has no special favour as a task, and the second that an index derived from it is not obviously a measure of lateralization of cognitive function.

In response to the former come the observations at the end of chapter two, regarding the conflict between internal and face validity. Box-marking as a skill is clearly tapping-in closely to the sort of performance biases that characterise writing-hand preference, the biases of primary interest. In response to the latter comes the observation that all relationships in this field are very noisy ones, with few obvious confounders; the presence of a relationship between this measure of functional sided difference and cognitive function is of itself the finding of interest.

The 'handicapped group story', as has already been mentioned, is not new, and does not seem resolvable in this context. The female superiority on verbal testing is well-attested elsewhere in the literature (see Halpern 2000 for review).

Data presentation

The data are presented as an exploration, rather than the testing of a hypothesis. This is, of course, a matter of intention and/or degree, as any presentation of data, even a frequency table, will make underlying assumptions of homogeneity. Even a list could be said to facilitate one particular interpretation of the data eg. that there are too many points to make sense of!

The plot of mean verbal ability against decile bins of laterality index were an attempt to get better 'resolution' on the issue of cognitive function versus a measure of functional lateralization. Means of cognitive performance by writing hand preference had been equivocal, but the relative hand skill measure in a cohort of over 12,000 offered much higher resolution on the issue that had been capitalised upon previously. The dataset offered the prospect of putting into context Dr Crow's finding that schizophrenic patients as a population had lower than average mean cognitive score and lower relative hand skill score, which could be interpreted as an effect of decreased anatomical (from earlier work) and functional brain asymmetry. In this data, the relationship could be examined in terms beyond simple linear regression. As mentioned above, the use of ten bins in the initial analysis was perhaps fortunate, in that it showed the effect. It also allowed an analysis of polynomial trends (see paper), which supported the finding. It was, however, a less than ideal method of presenting the finding to a general audience.

The alternative technique used locally-weighted least-squares smoothing in SPSS (Cleveland 1979), regressing the y-values on x using a 'moving average': as one moves away from the point on the x-axis under consideration, the contribution of data points to the mean decreases exponentially. This continuous estimate has the advantage of robustness in the face of outliers, and no a priori hypothesis about the distribution of the points. At the very least this approach produced plots with the point of equipoise at the centre of the x-axis.

The exact 'hairiness' of the plots was determined by the width of the smoothing window, as determined by coefficient alpha (the proportion of points subjected to the exponential weighting), and the number of iterations employed. The general trend of the plot seemed best served by values of alpha=0.5 and 3 iterations, the software default. Larger values merely made the plot flatter. Smaller produced small bumps that were inconsistent between the cognitive tests employed. This judgement rests on 'how bumpy one expects the plot to be', bootstrapping the concept of what one is looking for.

Locally-weighted smoothing is still just regressing y on x, however, and thus can be confounded by non-homogeneity. However, the division of the findings into hand preference groups goes no small way towards removing the most obvious non-homogeneity present in this data, the division by writing hand.

PAPER 2: "HOW FAR DOES THE BRAIN LATERALIZE?: AN UNBIASED METHOD FOR DETERMINING THE OPTIMUM DEGREE OF HEMISPHERIC SPECIALISATION" Leask & Crow 1998.

Introduction

The confounding factors mentioned in previous chapters are varied - problems making measurements, conceptualising the measurements, and conceptualisation of 'lateralization'. This second paper described the discovery that a further source of confounding, regression to the mean, had been clouding the field for over a decade.

The problem

There was a curiously unsatisfying aspect to hand performance measures in the NCDS. We could demonstrate a relationship between RL difference and other intellectual performance, at least as far as a dip in performance around zero, and better performance away from zero (towards the population mean). This made some sort of sense as far as selection for fitness 'via' selection for hand asymmetry, or an asymmetry linked in some way to this. However, there was no such relationship between RL difference and hand performance itself.

This could be explained away by saying that the link between verbal processing asymmetry and handedness asymmetry (centrally) was so important, that selection for facility at this completely overrode selection for hand skill as a phenotype. In this respect the basic relationship seen in NCDS box-ticking data was reassuringly similar to the relationships seen in data from other respected workers (Galaburda 1987, Annet 1990, Tan 1990, 1992b-e).

In all cases this was interpreted 'straight off the graph'. There appeared to be a fundamental quality to the development of asymmetry, structural or functional: "Dominance is achieved by deterioration of the non-dominant side, rather than maximisation of the dominant side" ie. the performance dives away from zero on the non-dominant side, but stays constant on the dominant side. This understanding had formed the basis of several theories of the development of cerebral asymmetry (Galaburda 1987, 1990).

However, the scatterplots generated by plotting performance against laterality looked curiously-distributed for noisy data, with local un-evenness in distribution, up to what appeared to be limit-curves (see figures in Leask & Crow 1998).

The obvious way to clear the air was to put random, rather than experimental, data, into the process of generating such a figure, thus demonstrating that what was seen was a consequence of the distribution of the data in question, and not an artefact.

The result of this came as something of a shock. It generated graphs of mean performance by laterality that appeared all but identical to those derived from real data. Asymmetry was developing completely randomly in each half of the brain. A profoundly unsettling idea.

The explanation for the similarity between real and random-data plots lies in the fact that, in such plots, one is not plotting two independent variables. The Y variable (R) is plotted against the X-variable, which is a clearly-defined function of R as well (Y=f(R,L)). Given noise in R and L, what one sees on regressing Y on X is the distribution of the function itself. In this case the distribution of (x-y)/(x+y) for all values of x & y. R & L are fairly normally-distributed if grouped by writing-hand, and if one puts in normally-distributed, random data, one gets plots that look even more like the real data.

Under usual experimental circumstances, one defines a dependant and an independent variable, and explores what happens to the dependant variable when the independent variable changes. However, in handedness research the poor correlation between different measures of relative skill are legend, so plotting a measure of hand skill against a laterality index derived from another measure would be even more difficult to interpret.

In essence, then, what people had been doing was attempting to interpret a 2D plot with only 1½ variables. Without knowledge of the distortion that regression to the mean would induce in the distribution, interpretation is tricky, if not impossible. More data is required, or the plot is meaningless. Any conclusions drawn from such spurious interpretations will share this fate.

A solution
In a typical scatterplot, uncorrelated XY data will form a uniform cloud. Regression of Y on X will produce a straight, horizontal line. The 'real' mean, we then interpret by comparison with a horizontal reference (a null hypothesis, in our head), in order to conclude "It's going up", "It's straight", or "It's going down". This is <u>not</u> the case here. The null hypothesis is not a straight line.

Given the restriction that another index could not be used, an alternative approach was employed. The near-normal distribution of the hand skill values by writing hand meant that it would be possible to 'model' the data, with one difference; one could create right- and left-hand values that were uncorrelated. Using these to generate a 'reference' performance and laterality index, one could then propose a null hypothesis:

"Is there evidence here that real performance deviates from that which we'd see if the data were random, and if so, where and in what direction?"

A plot combining real and random, reference data could test it.

The superficially more attractive hypothesis is that symmetrical development is perturbed. A reference line for this has all reference cases lying on a vertical line at zero. The answer to the question: "Is there evidence on this plot that hand performance deviates from that which we would get if development on each side identical and if so, where?" would be "Yes. For all values of index $\neq 0$". This rather stultifying conclusion is reminiscent of asking someone "Where am I?", to be told "Standing in front of me". We therefore tested the hypothesis that would yield useful information about the relationship between performance and non-zero values of laterality.

This modelling approach produced the results seen in the paper. The deviations due to correlation greater than zero were, in some ways, surprisingly small. On the other hand, the variance accounted for by writing hand was clearly huge. What remained was intriguing - for the first time such a curve could be interpreted correctly, that performance in both hands is being maximised, above that which would be obtained by no correlation, near the values of laterality index that were maximised in the population. Performance drops off at extremes of the population distribution. It makes sense, in a way previous erroneous interpretations could not.

Conclusion

The findings were that a measure of functional lateralization shows an interesting relationship with higher intellectual function, that ties in with theories of handedness, language and psychosis. One interpretation of the unconfounded plot of hand performance and lateralization is that performance is being maximised in the population by selection of an optimum degree of lateralization. It would follow then that magnitude of lateralization (notwithstanding fluctuating symmetry) is under genetic control.

The distance between the lateralization point of maximum performance, and the lateralization most common in each population, could suggest linkage of hand performance to some even more highly-lateralized function.

The key achievement was to replace a baffling relationship with one that made more sense in terms of selection. That it asked further questions was not a surprise. It does not seem to shed light on the origin of the R-bias in the population.

Chapter summary

Used with care, laterality indices can show simple relationships to measures of higher intellectual function, that make sense in the context of theories about handedness, language and psychosis.

It can be observed however that technical problems have led to the obscuring of an important relationship, between performance at and lateralization of a task, for over a decade.

Chapter 8: RL measures in NCDS & BCS70 - a description

Extending the analysis to two cohorts and two measures

This chapter will extend the scope of the work presented in the previous chapter, comparing results between different measures of performance, and different cohorts. It goes on to present results from an approach that avoids laterality indices, and ends with a comparison of the results.

1. Refining the analysis - using laterality indices

Introduction

Fairly straightforward relationships between performance measures by hand and cerebral function had been demonstrated, after accounting for the 'regression artefact' which can result from the use of a laterality index.
Two avenues were suggested by this finding. Firstly, what would one see using these techniques applied to other measures, or other cohorts? Are we seeing something specific to one test, or lateralization in general? Secondly, given that methodological problems remain, what would one see if one avoided laterality indices altogether?

Hand performance in two measures
One criticism of the paper on hemispheric indecision was that it only explored one of the performance measures in the NCDS, box-ticking, and ignored the other, match-picking. It was clearly time to have a look at match-picking because it was there.

Three tests of performance by hand in the NCDS?
The third performance measure by hand in the NCDS, counting how many times out of ten a ball was caught by each hand, was very skewed indeed (Table 1). This poorly-distributed variable tells us something about catching in general - on the whole pretty good - and is of use in determining which cohort members were clumsy at this. A log-plotted histogram (Figure 1) shows a midline ridge of sorts, visible in the table. However, with about 90% of children scoring 9/10 or more with each hand, its value as a continuous measure in the population was very limited.

RH / LH	0	1	2	3	4	5	6	7	8	9	10
0	69	12	2	0	0	1	0	2	4	0	3
1	9	11	7	0	0		0	0	0	0	3
2	3	2	4	7	1	0	1	1	1	0	0
3	1	2	5	1	0	4	2	0	0	1	2
4	2	1	4	6	3	2	5	2	1	2	3
5	1	0	1	6	8	41	5	1	4	5	8
6	1	0	3	4	4	11	6	15	9	8	7
7	0	1	0	2	6	13	20	15	24	23	46
8	0	1	2	3	12	11	25	53	53	108	126
9	4	0	2	3	2	15	32	91	194	413	760
10	2	4	5	12	16	33	58	146	506	1693	7764

Table 1: Catches (out of 10) by right and left hands

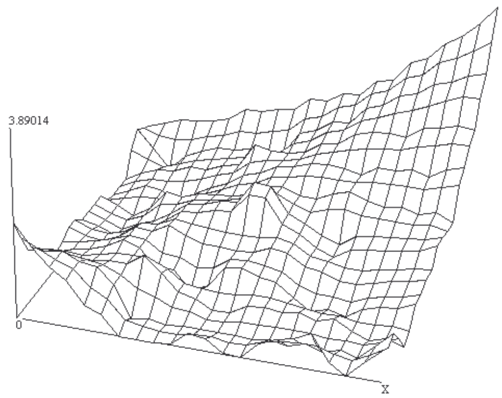


Figure 1: Log-plot histogram of data in Table 1.
- R & L catches out of 10 on X&Y, log(frequency) on Z

- Comparing results in two cohorts
The other criticism possible of any work in a cohort dataset is that the findings may not generalise to other populations, as cohorts are always tightly-defined in some way. In this instance, any findings could be said to only apply to individuals from the UK, of about that age, born around about that time of year. Comparison analyses in the 1958 and 1970 cohorts has already been performed in other areas (Bynner, Wiggins & Parsons 1996). The literature on changes in hand preference in with age suggests there might be some demographic shifts in hand preference as the century progressed (see chapter 3), so comparison with a group several years later would be nice.

Thus the following analyses were performed, comparing results from two measures of hand skill (box-marking and match-picking), in two cohorts:
- a refined analysis of hand performance versus laterality index
- a comparison of cognitive function and hand skill laterality index
- a comparison of hand skill by side, avoiding regression artefacts, and
- a comparison of cognitive function and hand skill by side,
the last two analyses avoiding laterality indices altogether.

1a. Hand skill versus laterality index

Methods

Measures
Data was taken from the NCDS dataset at age 11, and BCS70 at age 10.

NCDS
The measures were the same as those used in the first paper in Chapter 7, with the addition of the results of the match-picking task.

All cases scoring zero on any test for either hand were removed from subsequent analysis. This was because consideration was being given to the relationship between performance on each side, and a score of zero was felt to be too ambiguous: a subject can score zero without even commencing the task.

The match-picking task was measuring speed at picking up and moving 20 individual matches, by each hand separately, from one open matchbox to another. The data in the NCDS dataset was censored at 99 seconds, and censored data is awkward to deal with satisfactorily. In this instance the units of measurement were the reciprocal of those for box-ticking, ie. 'time per task' (ie. time for 20 matches), rather than 'task per time'(eg. matches per minute). It therefore seemed appropriate to transform the results into matches/minute, to allow direct comparison with the results from the box-marking task. This transformation also 'bunched-up' the censored results near the origin, decreasing their influence on the fitted lines.

It was also initially noted that holding and moving a pencil looked very similar to picking-up and moving a match; similar performance distributions were anticipated.

BCS70

Measures were used that were as similar as possible to those applied to the NCDS cohort eleven years earlier. The same transformation was performed on the match-picking results.

Statistics

Choice of laterality index: Despite the problems outlined already with a standardised index (R-L)/(R+L), a simple difference index (R-L) does not avoid methodological problems (see second paper in Chapter 7); indeed, in some ways it is even more misleading, as it has dimensions. In the interests of comparing results with the earlier papers, the standardised index was therefore used throughout.

The approach outlined in Leask & Crow was modified slightly. The original paper used a computer-generated normal distribution, with the same mean and standard distribution as the original data. This time, the analysis kept 'closer' to the original data by 'lagging' the lefthand data on the right to produce a descriptively identical but uncorrelated reference dataset.

The deviations seen between real and reference data were quite small. To explore whether or not these deviations were a consequence of chance, a number of alternative low-correlation reference lines were generated using an iterative algorithm that lagged right-hand performance on left, and generated a reference line if the correlation between the resulting measures were small (<0.01). These were all put on the final plots, so chance deviations between them could be compared with any deviations of the real data.

Results - Histograms

NCDS Preferred writing hand:		
Right	11149	88.6%
Left	1409	11.4%

BCS70 Preferred writing hand:		
Right	11288	88.7%
Left	1484	11.3%

NCDS Sex	Total cohort	With handedness data
Male	9890 (52.5%)	6500 (51.2%)
Female	8961 (47.5%)	6199 (48.8%)

BCS70 Sex	Total cohort	With handedness data
Male	8906 (51.8%)	6147 (51.4%)
Female	8279 (48.2%)	5822 (48.6%)

Table 2 - Distribution of sex and handedness in both cohorts.

NCDS Box-marking - matches in 1 minute

	Range	Mean (sd)
RH	6-200	89.4 (23.5)
LH	2-168	69.6 (21.2)
		p<0.0001

NCDS Match-picking - time for 20 matches

	Range	Mean (sd)
RH	10-99	44.0 (11.7)
LH	4-99	44.4 (11.6)
		p=0.007

NCDS Match-picking - matches per minute

	Range	Mean (sd)
RH	12-120	29.3 (8.6)
LH	12-300	28.9 (8.6)
		p=0.002

BCS70 Match-picking - time for 20 matches

	Range	Mean (sd)
RH	2-535	45.8 (16.1)
LH	2-490	46.2 (16.0)
		p=0.04

BCS70 Match-picking - matches per minute

	Range	Mean (sd)
RH	2-600	28.8 (12.1)
LH	2-600	28.3 (11.9)
		p=0.004

Table 3 - Hand skill measures in both cohorts.
(p = significance of difference between right hand and left hand performance)

NCDS Relative hand skill on box-marking - mean (sd)

	Male	Female	Difference	
Right-handers	15.88 (9.1)	16.55 (9.3)	0.07 sd	p=0.0001
Left-handers	-13.76 (10.3)	-13.68 (11.3)	0.007sd	p=0.9

NCDS Relative hand skill on match-picking - mean (sd)

	Male	Female	Difference	
Right-handers	0.72 (8.7)	1.3(8.6)	0.07 sd	p=0.0003
Left-handers	-3.74 (9.5)	-3.17 (9.3)	0.06 sd	p=0.27
	p<0.00001	p<0.00001		

BCS70 Relative hand skill on match-picking - mean (sd)

	Male	Female	Difference	
Right-handers	0.808 (8.9)	1.389 (8.8)	0.07sd	p=0.0008
Left-handers	-3.481 (8.6)	-3.16 (8.9)	0.04sd	p=0.5
	p<0.00001	p<0.00001		

Table 4: Relative skill indices in both cohorts
(with sex-difference (and significance), and significance of hand performance difference for match-picking)

Handedness and sex distribution consistent between cohorts
The rate of lefthandedness is remarkably similar between the cohorts, as are the sex ratios for cases with handedness data.

Match-picking consistent between cohorts
Findings for the match-picking measure are remarkably similar between the NCDS and BCS70 eleven years later. Even down to a problem in the data recording (see below).

Bimodal distribution in box-ticking, not match-picking
As has been demonstrated previously (McManus 1985), the box-ticking task separates convincingly into two near-normal distributions by writing hand. The match-picking remains a right-shifted apparently unimodal distribution, and dividing by writing hand results in a small but significant separation of means. Whereas the box-ticking task separates convincingly into two near-normal distributions, the match-picking remains a right-shifted apparently unimodal distribution, with little separation by writing hand. Smoothed point densities allow the separation of the distributions to be seen and compared between measures (figure 2a,2b,2c). It should be born in mind that histograms are 'rough' (eg. figure 4 & NCDS histograms in McManus 1985); to the extent that a Kolmogrov-Smirnov test tests the null hypothesis of normality, none of the distributions are normal.

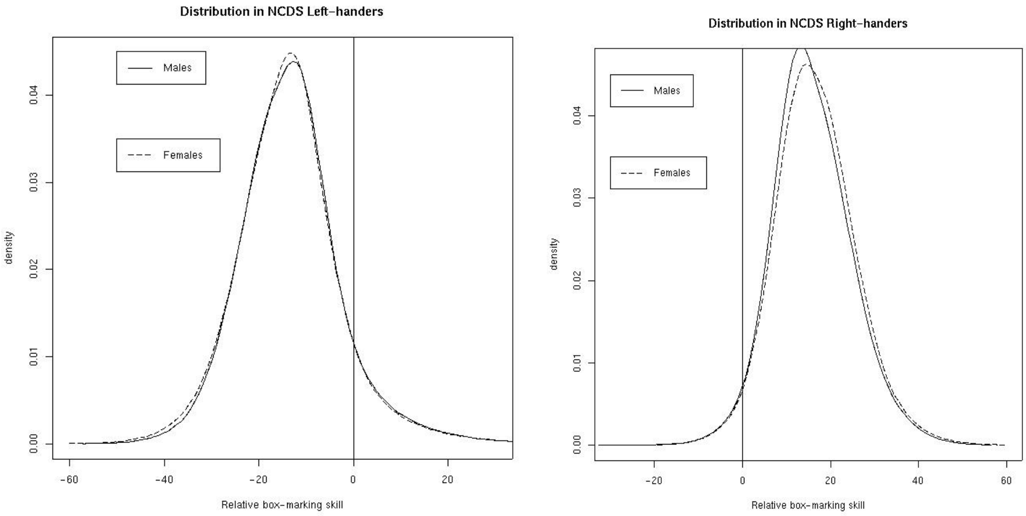


Figure 2a: Box-marking index divided by writing hand in NCDS

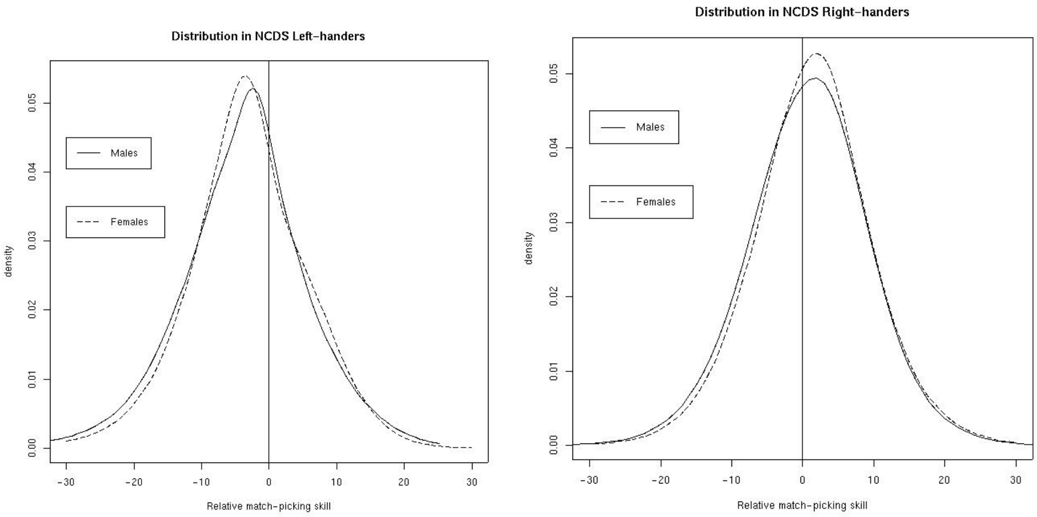


Figure 2b: Match-picking index divided by writing hand in NCDS

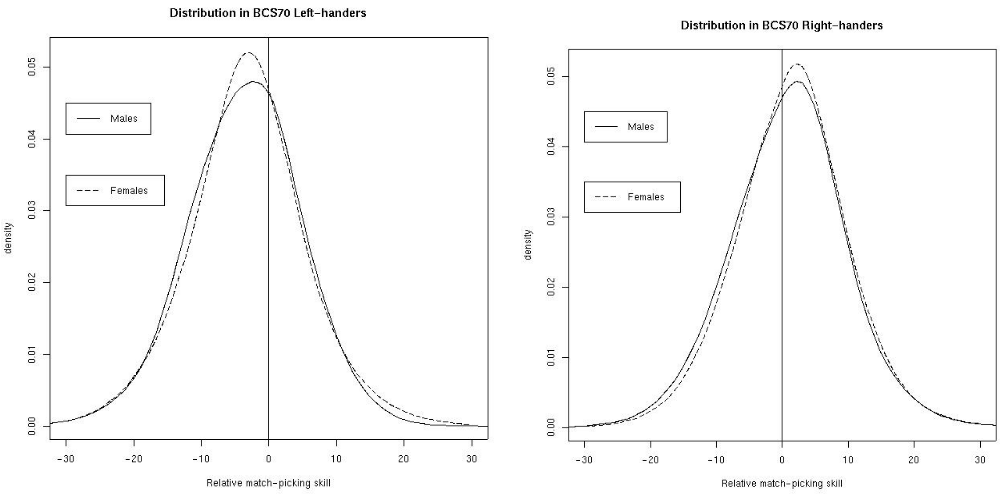


Figure 2c: Match-picking index divided by writing hand in BCS70

Sex-difference in distribution
There is a significant sex-difference in the means of righthanders, of the same order of magnitude in all the measures (0.07 standard deviations in all measures).

(Interestingly, if one calculates a non-standardised laterality index (R-L) for these data, this sex-difference rises to 0.15 sd for the box-marking task, which is similar to the 0.16 sd observed by Annett in her peg-boarding data (Annett & Kilshaw 1983)).

Multimodality in match-picking in both cohorts
In McManus' 1979 and 1985 examination of these data, he comments on the match-picking measure in the NCDS cohort dataset, noting that they are multimodal, with a peak at zero, with a bias towards timings being to the nearest five seconds. Intriguingly, this is the same in the BCS70 data (eg. Fig 3), resulting in the same large peak of relative skill indices around zero (Fig 4). However, this perhaps does not affect results overall. For example the sex-difference in this measure is consistent with that in the box-marking measure, with right-handed females more lateralized (by 0.07 sd) than right-handed males.

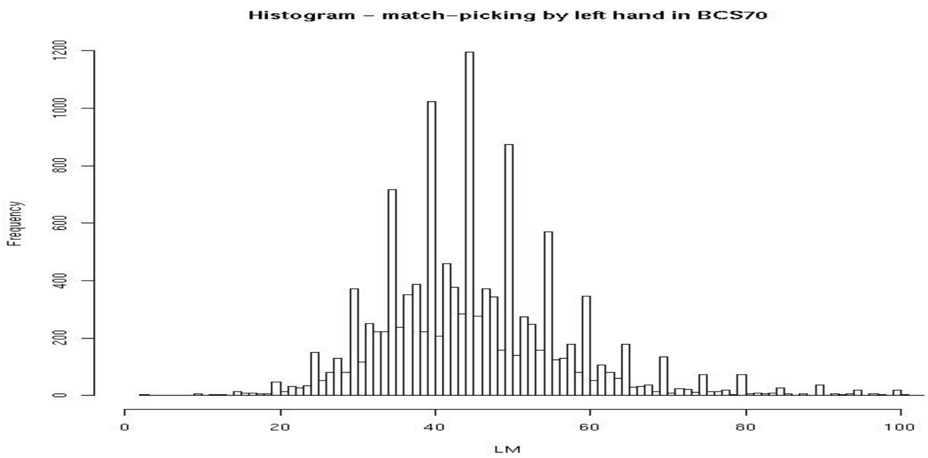


Figure 3: Match-picking scores for left hand in BCS70
Shows multimodality, times apparently rounded to nearest five seconds

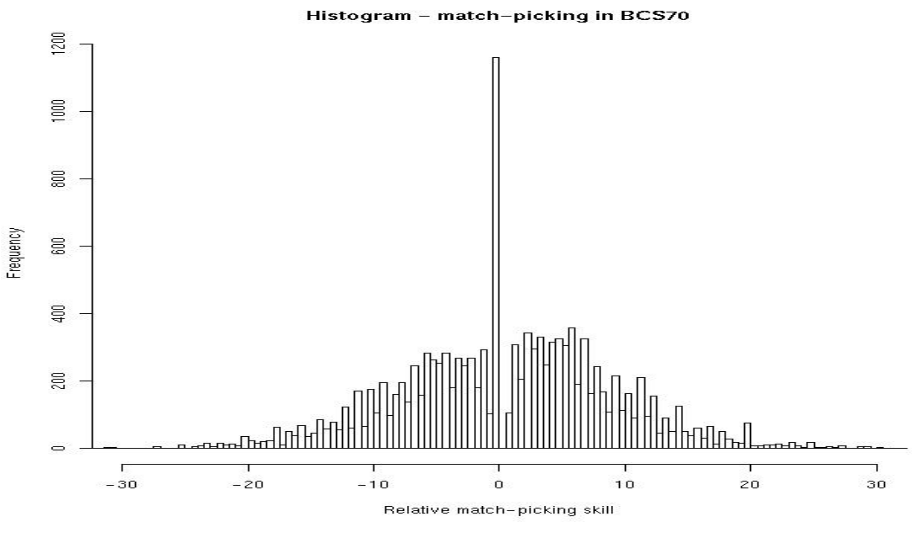


Figure 4: Match-picking index in BCS70
Shows peak at zero very similar to that in NCDS data.

Results - Locally-weighted smooths

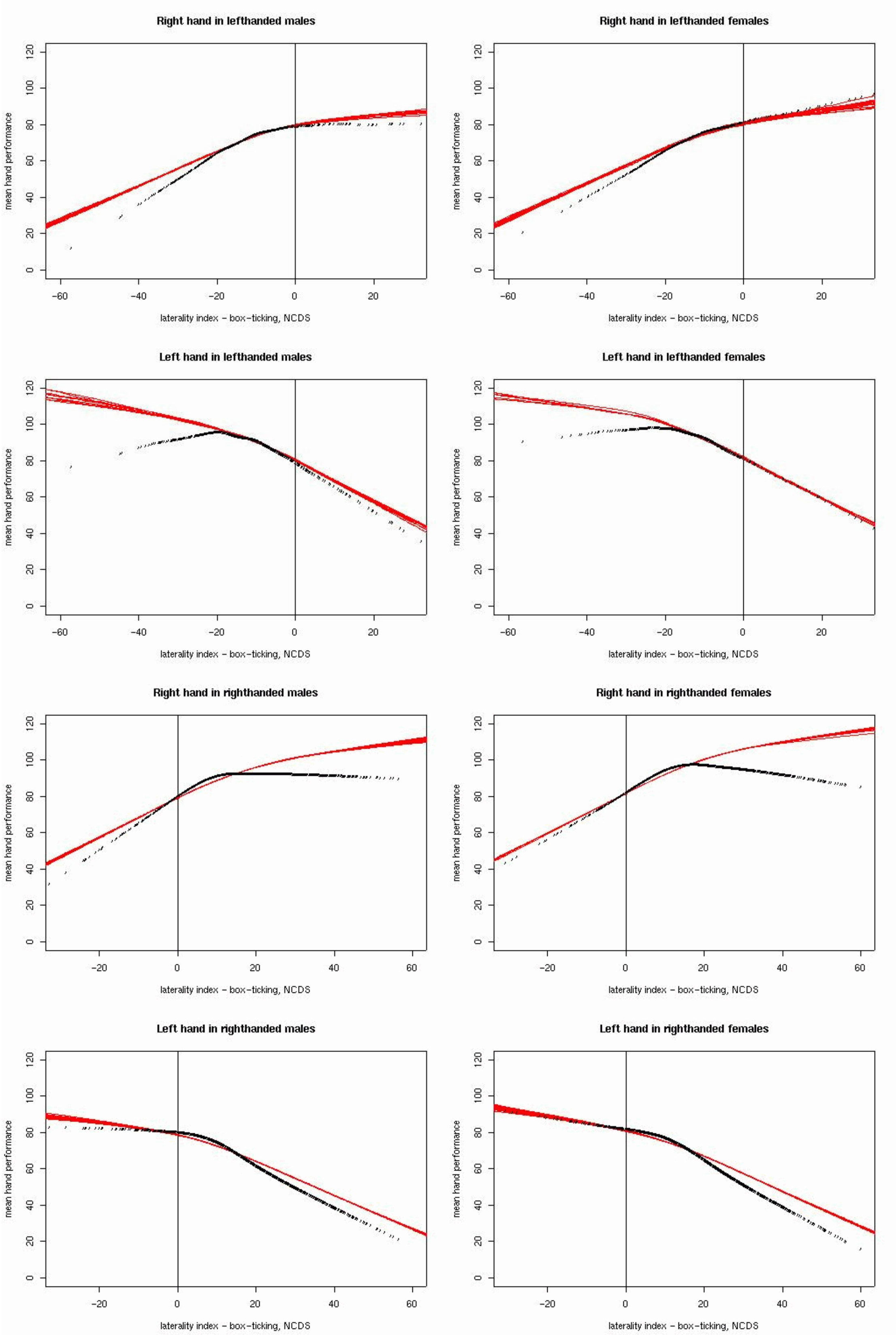


Figure 5a: Hand skill vs. laterality - box marking in NCDS
- Black marks - mean hand skill. Red lines - 'no correlation' reference lines

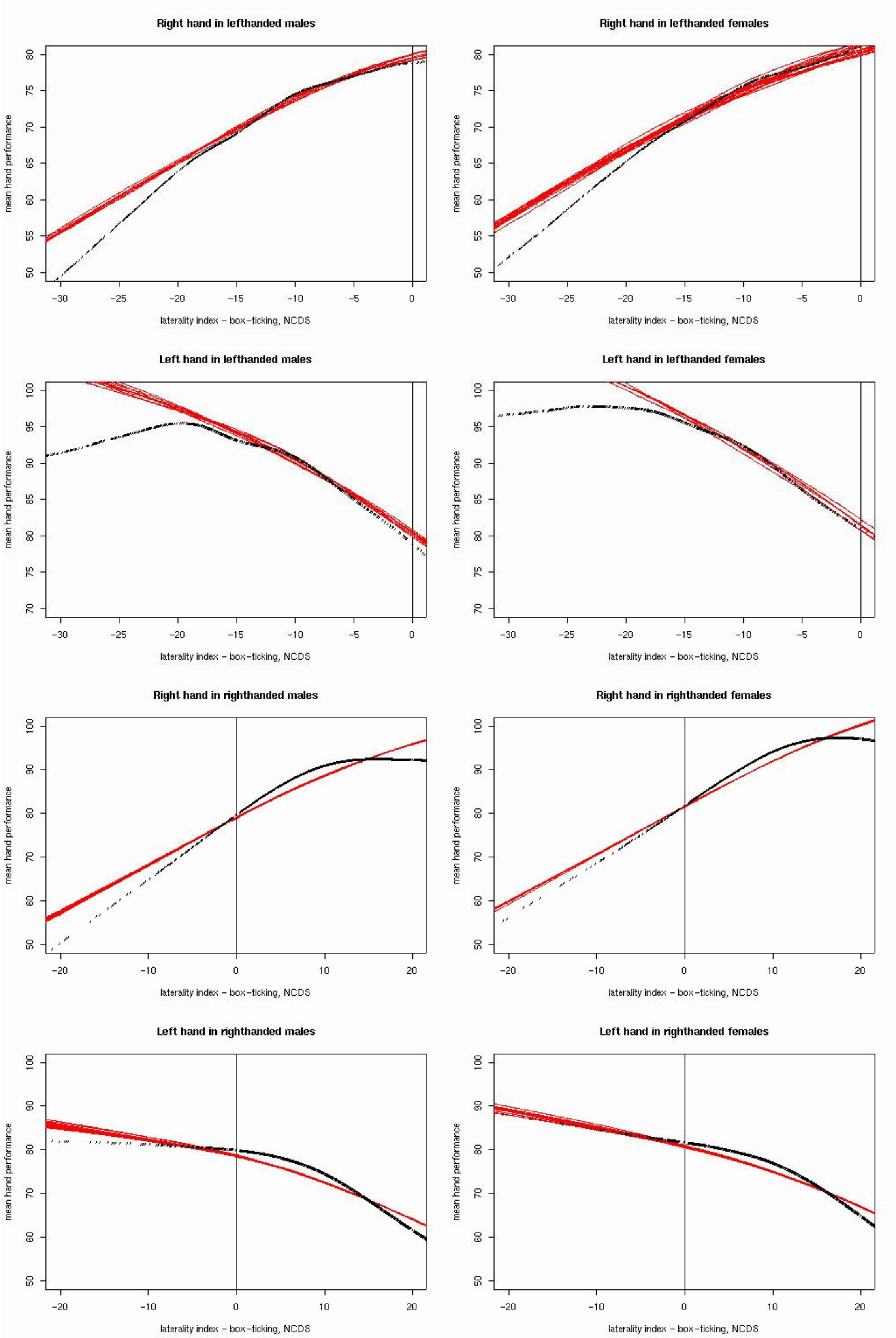


Figure 5b: Hand skill vs. laterality - box marking in NCDS - DETAILS

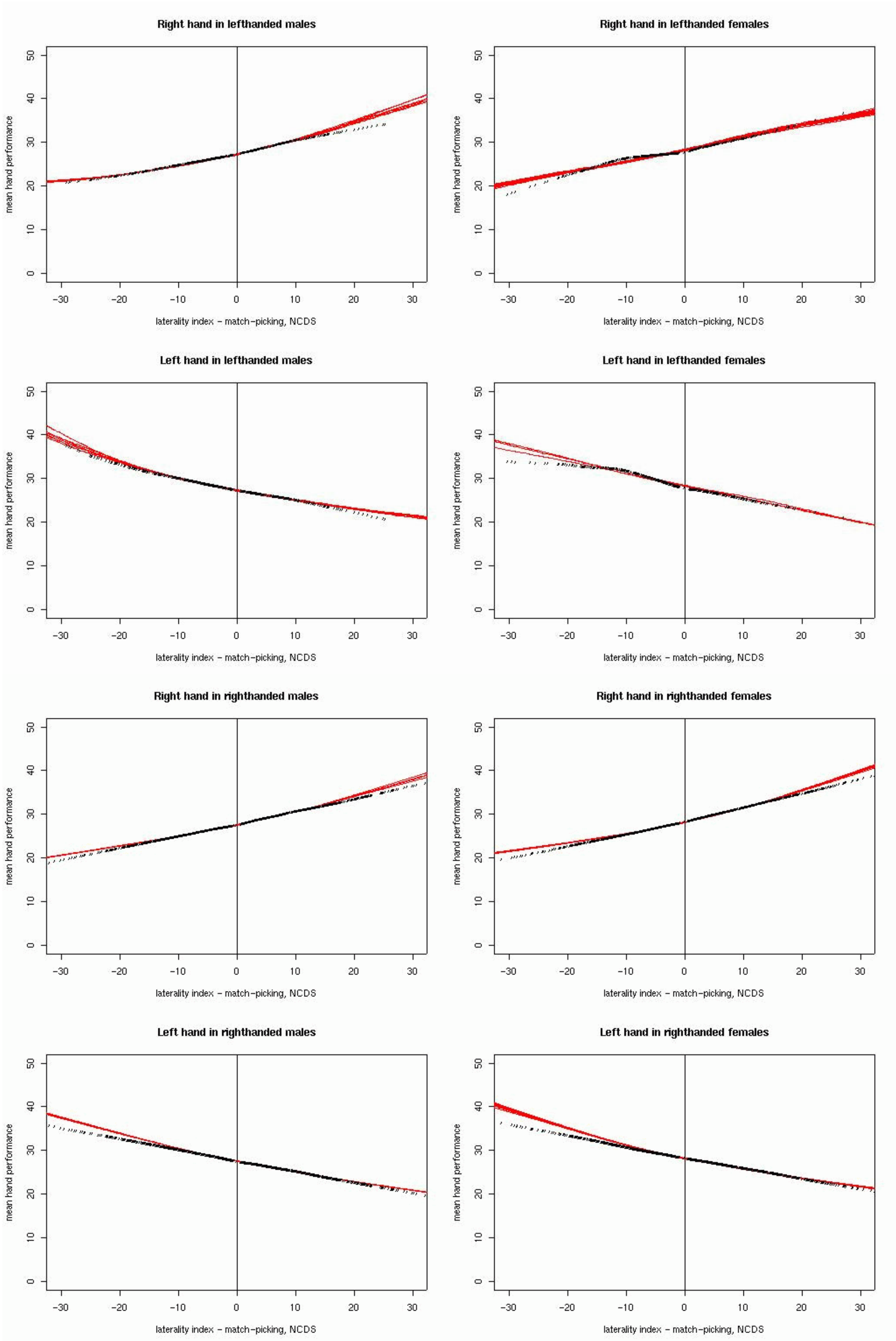


Figure 6a: Hand skill vs. laterality - match-picking in NCDS
- Black marks - mean hand skill. Red lines - 'no correlation' reference lines

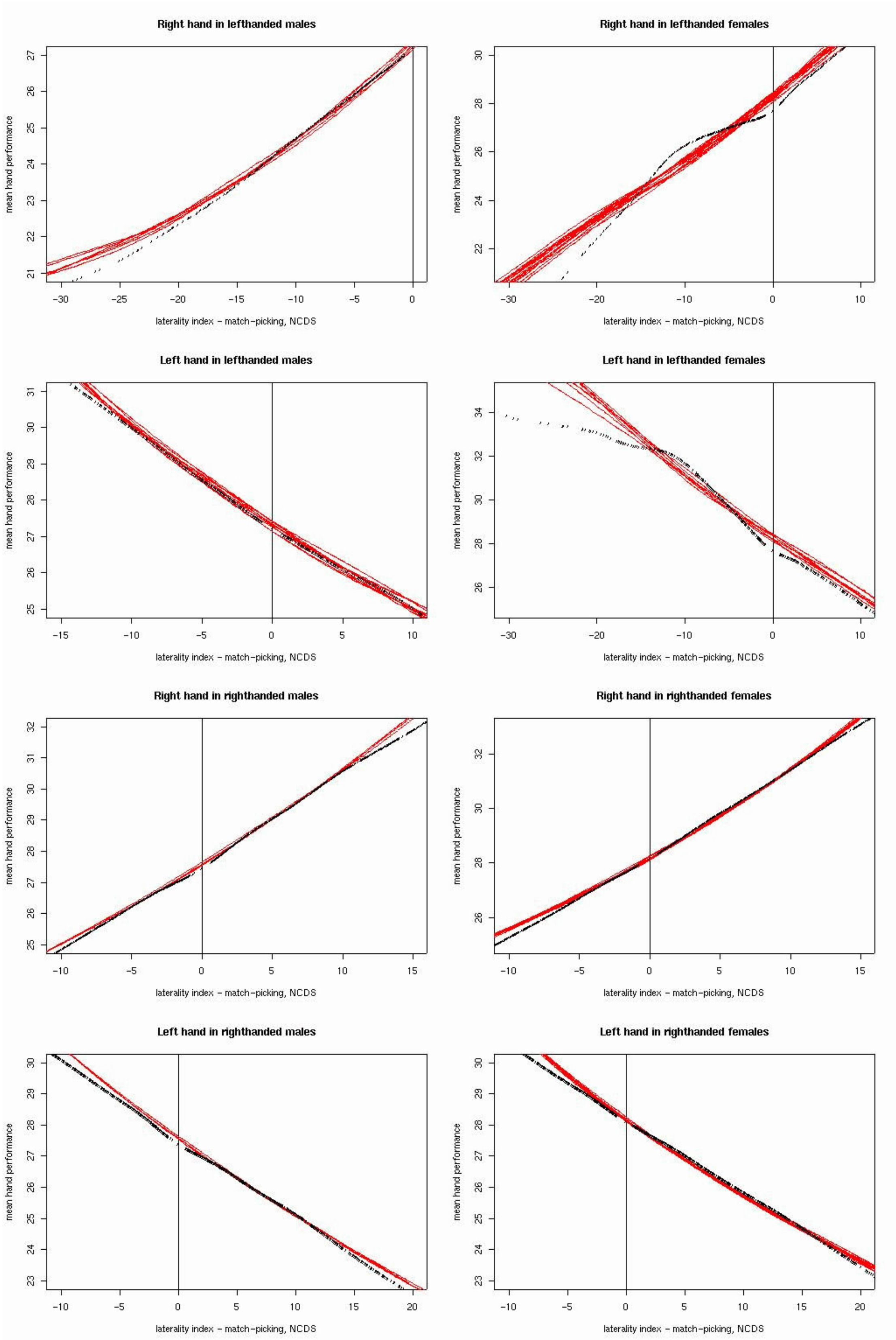


Figure 6b: Hand skill vs. laterality - match-picking in NCDS - DETAILS
- Black marks - mean hand skill. Red lines - 'no correlation' reference lines

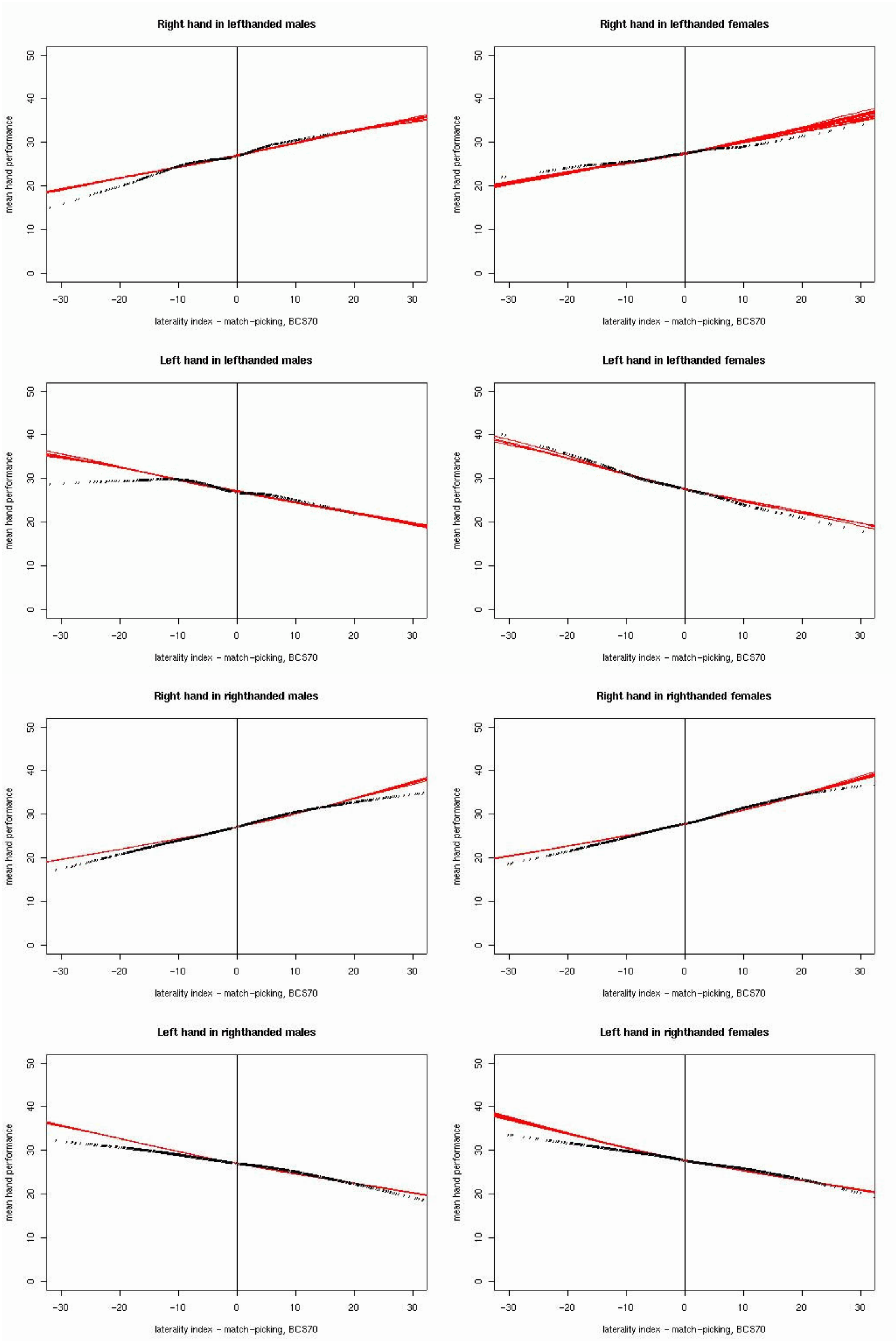


Figure 7a: Hand skill vs. laterality - match-picking in BCS70
- Black marks - mean hand skill. Red lines - 'no correlation' reference lines

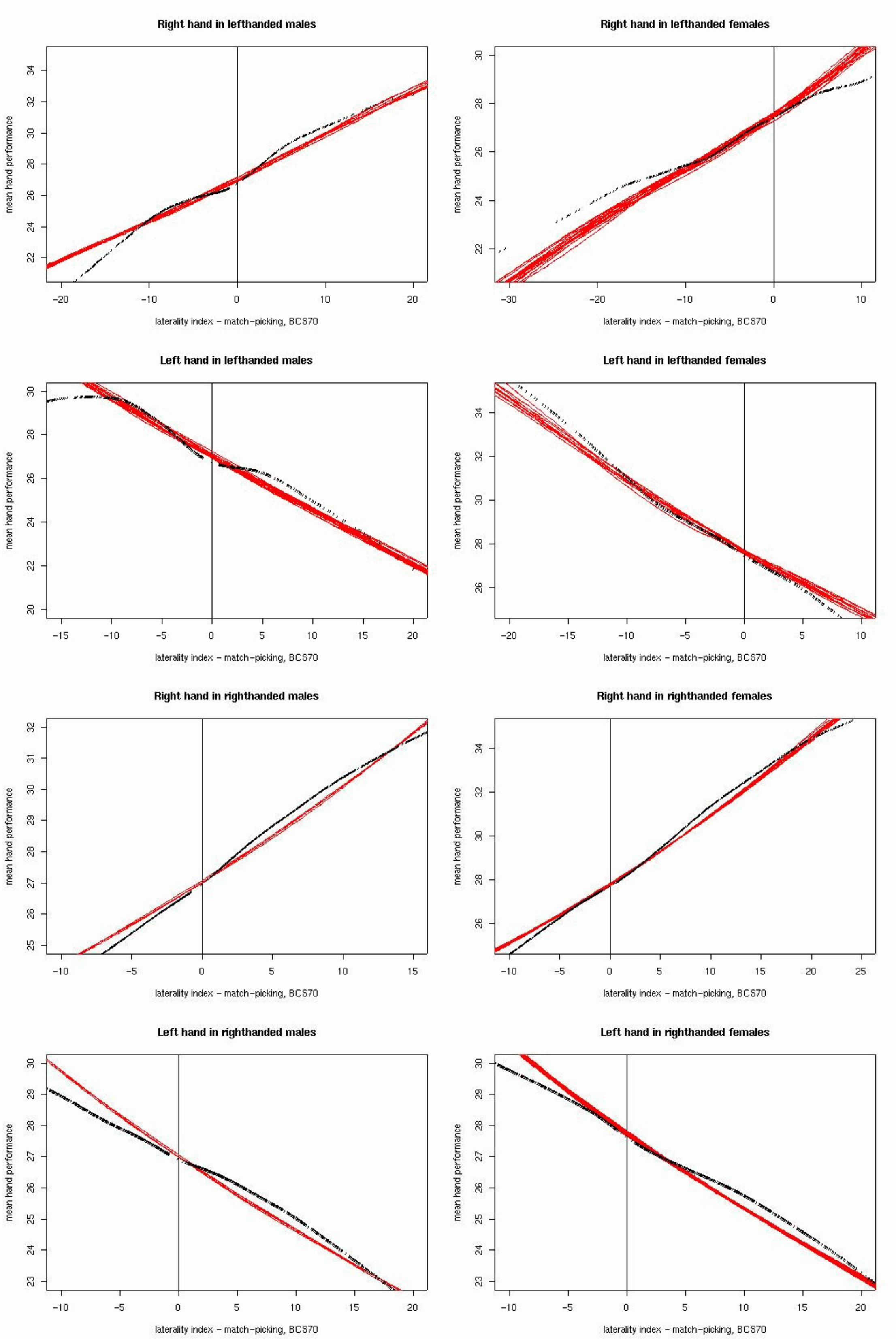


Figure 7b: Hand skill vs. laterality - match-picking in BCS70 - DETAILS
- Black marks - mean hand skill. Red lines - 'no correlation' reference lines
In summary:

Box-marking skill (figure 5):
This exceeds that which would be obtained if right & left-hand performance were uncorrelated for laterality values (~+10 for righthanders, ~ -10 for lefthanders) close to the population means. Performance drops off towards extremes.

The exceptions are the R&L hands of female lefthanders, where the deviation remains very close to the reference lines, perhaps just exceeding them at extremes of right-superiority. Numbers of cases are of course small at these extremes.

The multiple reference lines demonstrate that the reference line is stable towards the centre of the figures, and that deviations from it, although small, are significant. A quantitative estimate of the significance of such a trend is not strictly relevant, therefore: real data deviates from the no-correlation situation.

Match-picking skill (NCDS) (figure 6):
Where there is deviation, the trend is again approach of the real data from beneath the reference line to a maxima ~+10 for righthanders and ~ -10 for lefthanders, although even the eye of faith is perhaps straining in some instances (eg. left hand of lefthanded males). It is less clear in these figures that performance is exceeding the reference at any point, except perhaps the left hand of female right-handers, and both groups of lefthanded females. There is a slight hint at bimodality in several of the detail plots. Once again, lefthanded females seem anomalous at extremes of right-superiority.

Match-picking skill (BCS70) (figure 7):
There is more of a hint of bimodality in these figures eg. Both hands of male lefthanders. In the (larger) righthander groups the maxima are once more ~+10. Lefthanded females are once more anomalous, this time performance exceeding the reference for extremes of left-superiority.

Discussion

The findings contrast with previous, flawed interpretations of such plots. The impression that handedness derives not from superiority of the dominant hand but inferiority of the non-dominant hand is a consequence of a failure to appreciate how distorted 2D space on such a plot is, or how deceptive a plot of x vs. f(x) can be.

This analysis can also be viewed in the context of the 'noisy' nature of all these variables. A scatterplot of box-marking skill index vs. match-picking skill index looks like two blobs (Figure 8). Thus, apart from the separation of box-marking skill by writing hand into two groups, it is tempting to rule out any comparison between laterality on these measures altogether.

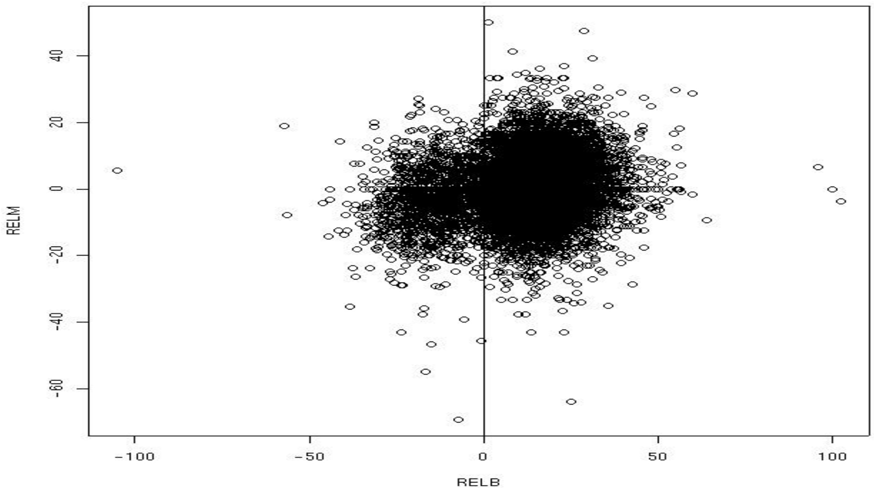


Figure 8: Scatterplot of box-marking versus match-picking laterality indices
- The poor correlation is clear. Beyond bimodality in box-marking, there are just two circular blobs.

1. All performances are falling off near the point of equal hand skill.

Fall-off at extremes are vulnerable to outliers. However, the fact that the trend is not for performance peaks around zero, even in match-picking, suggests the 'problems' around zero in box-marking do not merely reflect the separation in lateralization of the two populations. The optimum lateralization, for hand performance, is not zero.

2. Trends of deviation are reasonably consistent, with a consistent range of laterality values over which performance rises from less than to equal to or greater than that expected by chance in most instances.

As before, this suggests that the correlation (ordering of one side with respect to the other) is maximising function in both hands near the commonest values of RL difference.

3. After segregation by writing hand match-picking still shows trends towards bimodality, with increases in performance (relative to the reference line) on both sides of equal hand skill.

This approach makes it clear that handedness (writing hand) seems to segregate box-ticking performance into two populations, superiority in both hands being achieved towards the population mean. For match-picking the segregation is less informative; it does not appear particularly correlated with writing hand. Residual bimodality in the match-picking curves relative to their reference lines suggests that (unlike in the case of box-ticking) we have merely divided the match-pickers into two fairly randomly-chosen groups.

However, superiority of performance occurs at a laterality similar to that for box-marking. Standardisation of both measures into 'actions per minute' means that some quantitative comparison of the results is possible. Thus, once again the similarity between the laterality for maximum performance advantage, and the laterality most common in the population, cannot be avoided. Match-picking and box-ticking laterality are just poorly-correlated (eg. figure 8!).

4. Areas where performance exceeds the reference line are away from zero, but whereas population peaks are further out for box-ticking, they are much closer to zero for match-picking.

It is not at all uncommon for two tasks requiring fine motor control to produce poorly-correlated results (see chapter 3). Explanations for this usually rest in the different brain regions involved in the different tasks eg. practised versus unpractised tasks. There may be a mixture here, of fluctuating asymmetry, noise, and one or more continua/ handedness 'factors'.

However, there is a further observation to be made:

5. The deviations from reference line are greater for the box-ticking task than match-picking.

In both tasks, performance is maximised for both hands at a finite amount of laterality, remarkably consistent between tasks & cohorts, close to the population maximum for box-ticking, but not match-picking (where the maximum is close to zero). There is more of a performance boost in box-marking.

This may be a key point. For both tasks, performance is maximised in both hands for a similar amount of lateralization. However, in what can be argued to be a less-practised task, match-picking, the performance boost is small. In the practised task, the superiority of the preferred hand pulls the laterality values in the population over away from zero. However, the point for best performance doesn't seem to move – it is perhaps a property of the cybernetics of the brain. Practice 'selects' individuals for it. Without any 'selective pressure' for match-picking, the population distribution of skill remains random.

The greater performance boost suggests more practice in the box-marking task. The similar values of laterality index for maximum performance suggests this is hard-wired, a feature of the cybernetics of hand performance, not subject to the vagaries of practice. The different laterality index distributions tells us what values of index have been selected for; box-marking has, match-picking hasn't.

While the neuroanatomy of picking up matches is also quite different from that of using a pen, one could counter that that picking matches is like picking fleas: more highly-practised in less advanced cultures. Whether the population histograms for box-ticking and flea/match-picking would be reversed in more primitive cultures is an interesting but unknown question. We know that the right-preference is constant, and that hand preference for both these tasks is 9:1 R:L, but have no data for the distribution of hand skill over history.

The issue of ethology reminds us that the exact task under consideration is key; the cerebellar priming for even such tasks as similar as match-picking and box-ticking are clearly separate in terms of practice effects. The relationship of performance to lateralization seems independent of this.

If ability is under selection, performance peaks will most closely reflect population peaks for those tasks that are under selection. There appears to be a systematic bias here, as population peaks for laterality are further out still. It may be that the ability under selection performs better at an even greater degree of lateralization than hand skill.

Critique
There remain at least two problems with this technique, however:

1. The hypothesis under test relates to correlation between right and left - the 'other' independent variable in this set-up. While the principle seems sound, it relies on very large numbers to keep the variance of the reference line down. In smaller datasets, distinguishing any meaningful trend in the 'real' data over the reference would be impossible. The anomalous findings in the female left-handers in some plots are inconsistent, warning of the noise in these variables.

2. Problems remain with the distribution of the function (R-L)/(R+L) & smoothing. The function is discontinuous around zero (see plots in Chapter 7), and thus use of a uniform smoothing function is questionable. However, the data at either side of zero is also arbitrary. Difficulties remain in the interpretation of laterality indices.

Conclusions

Hand skill and laterality index
There appears to be a degree of lateralization, +10% or -10% of total range, which is associated with optimum hand skill. In both hands. On both measures. This may be some quality of the cybernetics of a lateralized skill.

The effect size is greater in box-marking, the more practised task, but the effect is there in match-picking too. It is not the same degree of lateralization as is maximised in the population for either measure - population means are greater for box-marking, and less for match-picking. Thus lateralization of these measures may be imperfectly linked to some more-lateralized function that <u>is</u> being selected for, perhaps language.

1b. Cognitive function versus laterality index

Methods

As above, right & left-writing groups were considered separately. LOESS smoothing was applied, by sex, this time including 95% confidence intervals.

All cohort data were extracted from archive datasets, re-coded as appropriate and merged into appropriate sets of variables using the statistics program SPSS v7.5 running under Windows 95 OSR2. Descriptive statistics and figures were generated using Splus 2000 running under Windows 95 OSR2, and "R" v1.2.1 running under Slackware Linux v7.1, and any associated libraries (eg. Locally-weighted smoothing was performed using Clive Loader's LOCFIT library).

Results

NCDS Verbal score on general ability test (/40)

	Range	Mean (sd)	
	0-40	22.1 (9.4)	
Males		21.0 (9.5)	p<0.000
Females		23.1 (9.1)	
RH		22.3 (9.3)	p<0.000
LH		21.4 (9.5)	

NCDS Non-verbal score on general ability test (/40)

	Range	Mean (sd)	
All	0-40	20.9 (7.6)	
Males		20.8 (7.7)	p<0.05
Females		21.0 (7.5)	
RH		21.1 (7.6)	p<0.005
LH		20.5 (7.4)	

BCS70 Verbal score on general ability test (/40)

	Range	Mean (sd)	
	0-41	28.2 (4.3)	
Males		28.5 (4.4)	p<0.000
Females		27.8 (4.2)	
RH		28.2 (4.3)	p=0.83
LH		28.2 (4.3)	

BCS70 Non-verbal score on general ability test (/40)

	Range	Mean (sd)	
All	0-28	15.5 (5.4)	
Males		15.2 (5.4)	p<0.000
Females		15.8 (5.3)	
RH		15.5 (5.4)	p=0.18
LH		15.3 (5.3)	

Table 5: Descriptive statistics of NCDS & BCS70 IQ measures.

Test characteristics (table 5):

The most surprising finding is that females have superior verbal skill in the NCDS, but males have superior verbal skill in BCS70.

All the measures were well-distributed with little skew, although there is some kurtosis in NCDS verbal skill (Figure 10).

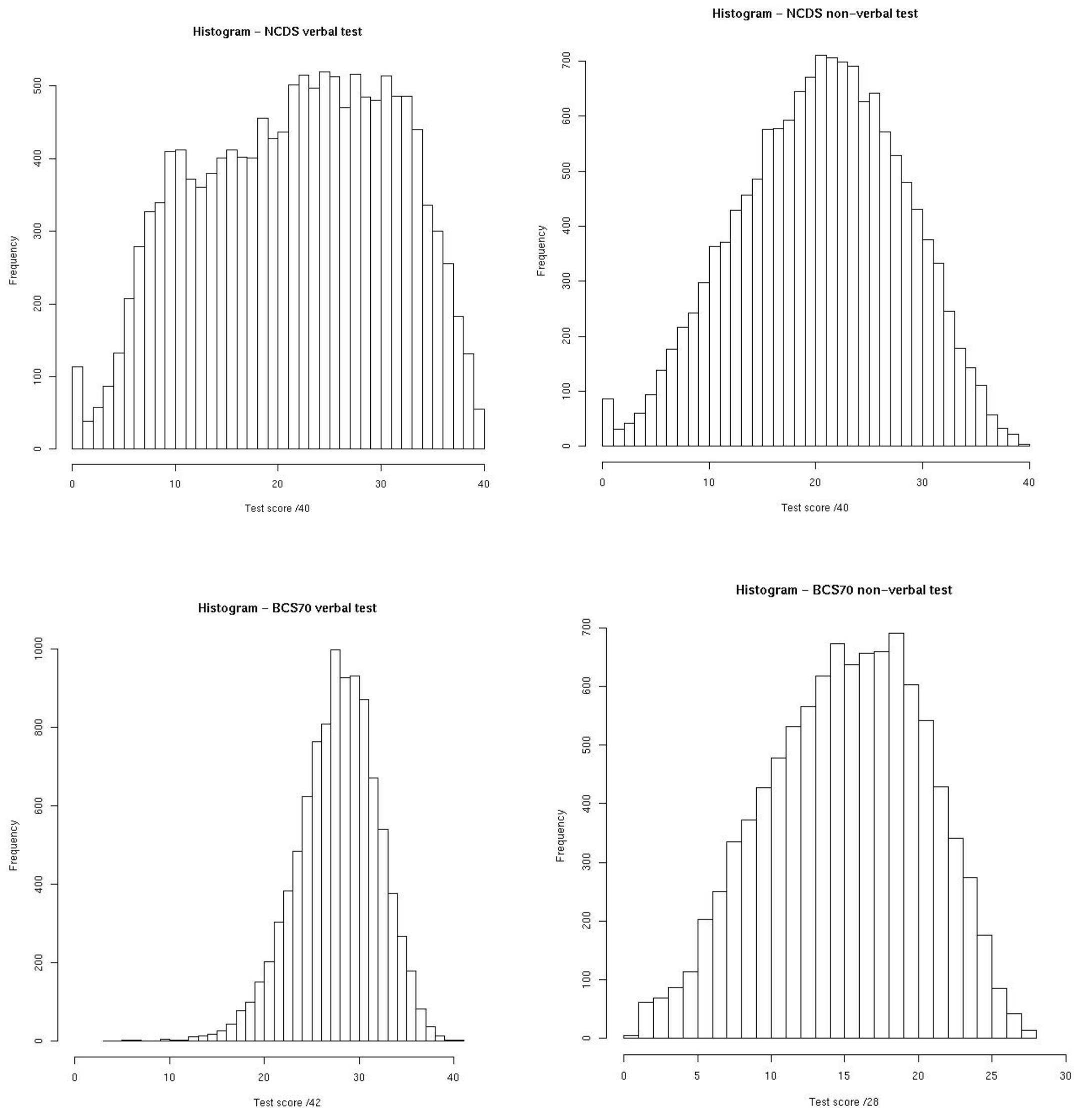


Figure 10: Histograms of verbal & non-verbal tests in NCDS & BCS70

Figures of mean verbal & non-verbal ability versus the available laterality indices are shown in figures 11a,b &c. Females are in blue. The 95% confidence intervals are the dotted lines.

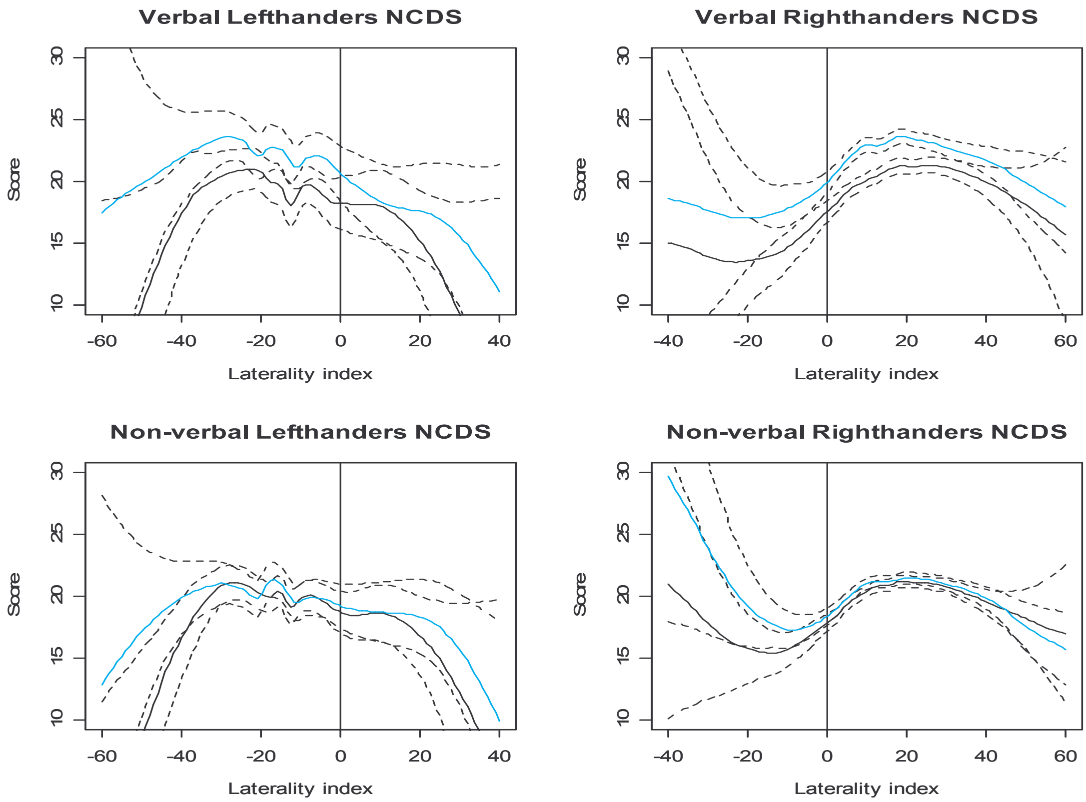


Figure 11a: Verbal & non-verbal ability in NCDS vs. box-tick laterality
(Males black, females blue. Dotted lines = 95% ci)

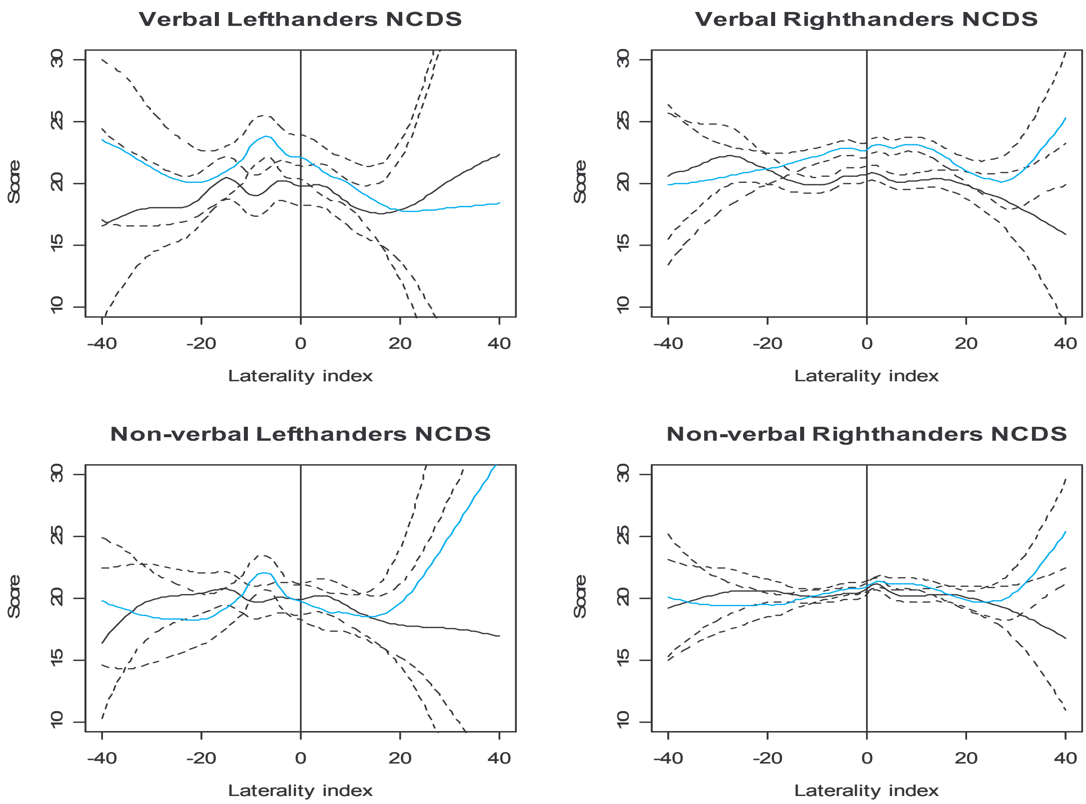


Figure 11b: Verbal & non-verbal ability in NCDS vs. match-pick laterality
(Males black, females blue. Dotted lines = 95% ci)

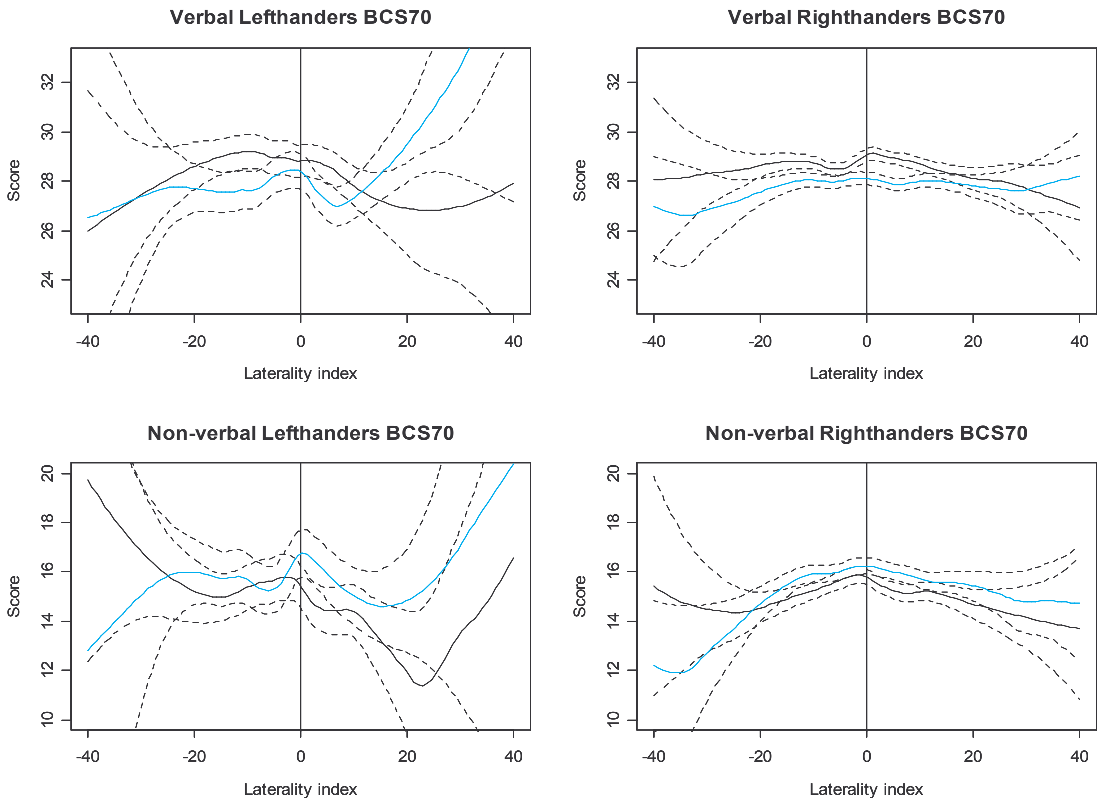


Figure 11c: Verbal & non-verbal ability in BCS70 vs. match-pick laterality
(Males black, females blue. Dotted lines = 95% ci)

NCDS verbal & non-verbal tests vs. box-marking laterality:
As with hand skill, peak performance is away from zero, although for verbal skill the peaks are closer to +/- 20 (righthanders & lefthanders respectively). There is little evidence of bimodality, so once again writing-hand seems to be dividing the population into two distinct groups. Overall performance falls off at extremes; the upswings in righthanders below -20 must be considered in the context of the small numbers of cases and broad confidence intervals. The female verbal superiority seems sustained across the range of laterality values.

NCDS verbal & non-verbal tests vs. match-picking laterality:
The plots are fairly flat. With the eye of faith one can see some suggestions of dips at zero (especially in females), but this is not impressive; if anything the overall trend looks more like a peak around zero. There is female verbal task superiority, again sustained across the range of values of laterality index.

BCS70 verbal & non-verbal tests vs. match-picking laterality:
Again fairly flat, with either a small dip in the middle, but the trend being to peak at zero. Male verbal task superiority shows little relationship to laterality.

Discussion

Drop-off of performance at extremes of lateralization
In both measures, a drop-off in performance can be seen at extremes of lateralization, in both directions. This finding is of interest, as it might be felt to support the notion of 'heterozygote advantage' proposed by Annett (Annett & Manning 1990). What can be seen here is that extreme degrees of lateralization are consistently associated with a handicap.

However, the finding remains vulnerable. Extreme laterality values could derive from extreme handicap on one side or the other (leading to a small denominator); a small number of handicapped individuals could bias the results.

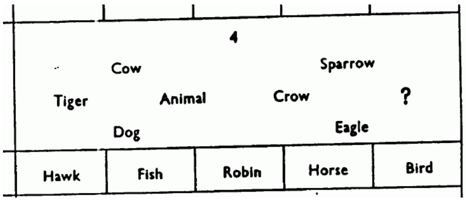
Box-marking segregates convincingly by writing hand
The box-marking task also demonstrates problems around zero (where right and left skill are approximately equal), a feature absent from match-picking. As in the 'Hemispheric Indecision' paper (chapter 7) this provides some face validity for partitioning box-ticking by writing hand, otherwise low performance at zero would pick up beyond it. Conversely, this suggests that match-picking skill is less meaningfully related to writing hand.

The dip around zero might be accounted for by a preponderance of otherwise poor-performers as a consequence of handicap (see McManus critique of dip at zero, discussed in chapter 7). In the tails of the distribution of normals, relatively small numbers of these groups could disproportionately affect the mean score eg. around zero laterality for the box-marking task. These same individuals, found near zero on match-picking would be swamped by the bulk of the un-displaced/practised normal population, and no dip seen. Perhaps that is what is seen here.

Match-picking segregates poorly by writing hand
As with hand performance, there are hints of bimodality in the match-picking plots, again suggesting this measure segregates poorly by writing hand.

Surprising reversal of verbal superiority by sex
The most surprising finding was the reversed sex-difference in verbal task superiority in BCS70 compared to NCDS, despite the tasks being superficially very similar. This is not entirely without precedent in the meta-analytic literature. For example, Hyde & Linn (1988) concluded that consistent measurable female verbal superiority exists in the literature only up to age six and beyond 25. Alternatively, this could be a real effect, ie. that over the 12 years between the tests, population performances changed, although there is no precedent for this, and other work examining smaller cohorts separated by up to 29 years, using identical tests for each cohort do not show any significant change in a significant female verbal superiority, over time (Goodman & Anderton 1997).

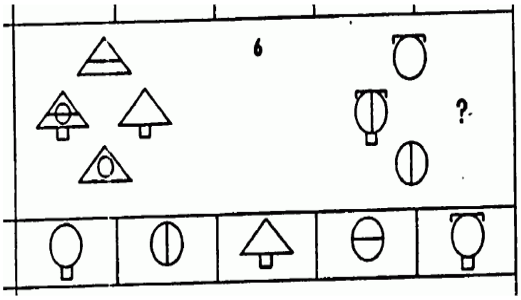
The literature is clear that gender differences are very sensitive to the exact paradigm under test (see Halpern 2000 for an informative review), and the differences between the resources under test in each cohort could account for the switch in group superiority. Example questions from the tests themselves can be seen in Figure 9 overleaf; the verbal tests are similar but not identical eg. in the NCDS task, children have to think of a word to go with the other 3, in BCS70 they have to choose from 4 alternatives. The NCDS task can be considered a test of receptive vocabulary, the BCS70 a test of expressive vocabulary.



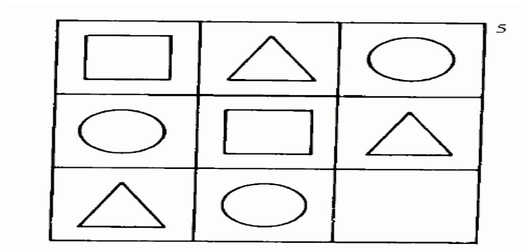
NCDS 'verbal' scale of general ability test:
- “Circle correct option in place of '?'”.

Item		
1	Red, blue, brown	
2	Milk lemonade, coffee	
3	Skirt, hat, trousers	
4	Lion, mouse, cow	

BCS70 'similarities' scale of British Ability Scale:
- “Name another group member, then add a group name”



NCDS 'non-verbal' scale of General Ability Test:
- “Circle the option that goes correctly in place of '?'”.



BCS70 'similarities' scale of British Ability Scale:
- “Draw in the 'missing' shape from the series”.

Figure 9 Verbal & non-verbal tests employed in each cohort .
The tests used from each cohort were matched for similarity.

Conclusions

Both the 'laterality' measures are related to higher intellectual functioning, both showing handicaps associated with extremes of lateralization. However, box-marking laterality accounts for more variance than match-picking laterality.

Interpretation of the dip at zero in the box-ticking measure remains ambiguous. Whether this is due to over-representation of handicapped individuals near zero, or simply where the two laterally-displaced sub-populations of right and left-handers overlap is unclear, and not resolved in this analysis.

2. Refining the analysis - avoiding laterality indices

Introduction

Throughout the analyses so far, the methodological problems with laterality indices can outweigh the advantages that stem from data-reduction. It therefore seemed appropriate to try examining this data using a technique that avoids the use of laterality indices altogether.

Avoiding indices might have several advantages, many of which are the inverse of the problems mentioned in chapter 1. The most obvious is the proximity one retains to the original measures. The presentation could be said to be more exploratory, more 'atheoretical' than one using laterality indices, without the implicit assumptions made in the construction of any such measure. Of course, an approach that is not testing a hypothesis remains as weak with this approach as with any.

2a. Avoiding indices - 2d scatterplots

Methods

The simplest formulation remains how right and left-hand performance compare. A scatterplot demonstrates this well (see Figure 12). However, once more, further summary is problematic. If we ask the question "What is the overall distribution of this data?", it is tempting to fit a line to it. We can even avoid prior assumptions about the distribution being along a straight line or a curve by using a locally weighted fit. However, that we still have a problem can be seen by comparing the plots of R vs L, and L vs R: Which is the dependent variable?

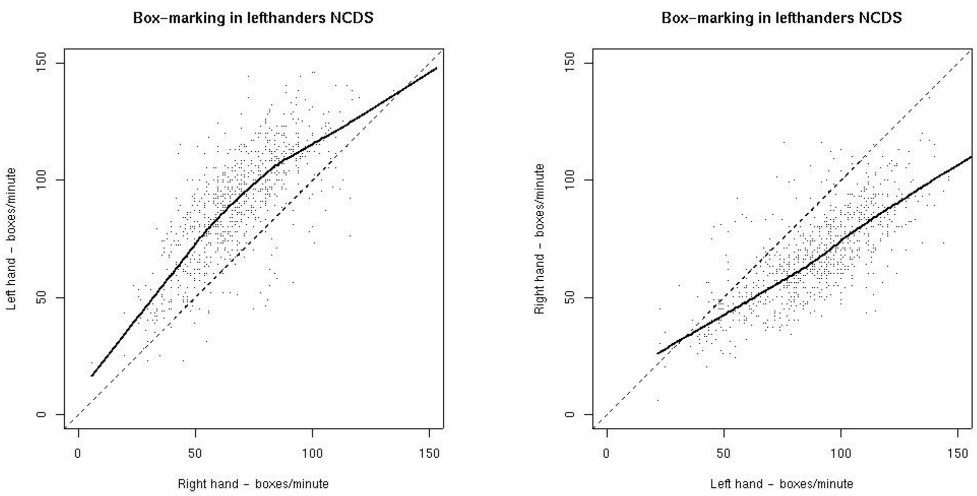


Fig 12. Right versus left, and left versus right hand performance scatterplots (in lefthanders).

- Note how the starting positions and trends towards the top-right are different for the locally-weighted smooth, depending on which is regressed on which.

It is clear that in the first plot:
- Preference matches skill advantage throughout the plot
- At upper reaches of skill, left-superiority is decreasing.

whereas the other shows:
- Low-ability individuals having preference the reverse of their skill
- At upper reaches of skill, left-superiority continues to increase

Once again we are in danger of misleading ourselves, as even a locally-weighted fit is regressing one variable on the other. Effectively, we are making an assumption about which is the dependent variable. In fact, for right & lefthand skill, such a judgement reflects social prejudice! They are both, effectively, independent variables.

Principal curve analysis
What is needed is a method that fits lines through the middle of the data in an orthogonal sense. Such a technique is principal curve analysis, which fits a line which is a nonparametric generalisation of a linear principal component of the data. The end effect is to remove the notion of which variable is being regressed upon, and the fits are orthogonal (see figure 13a & b).

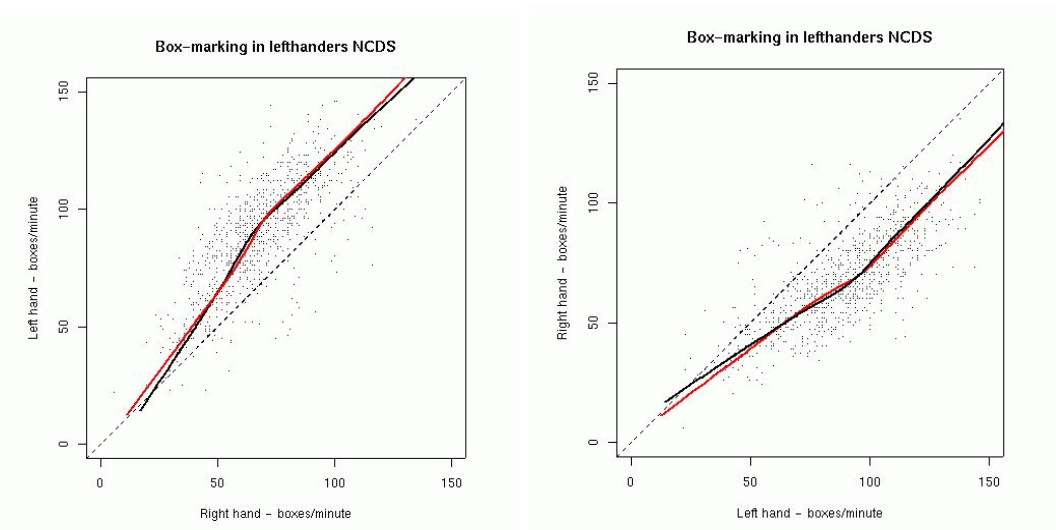


Figure 13. Two principal curve plots, with axes reversed. Note that the fitted line is now genuinely orthogonal ie. its path is independant of which way around the variable are on X and Y axes. Black = males, red = females

Results

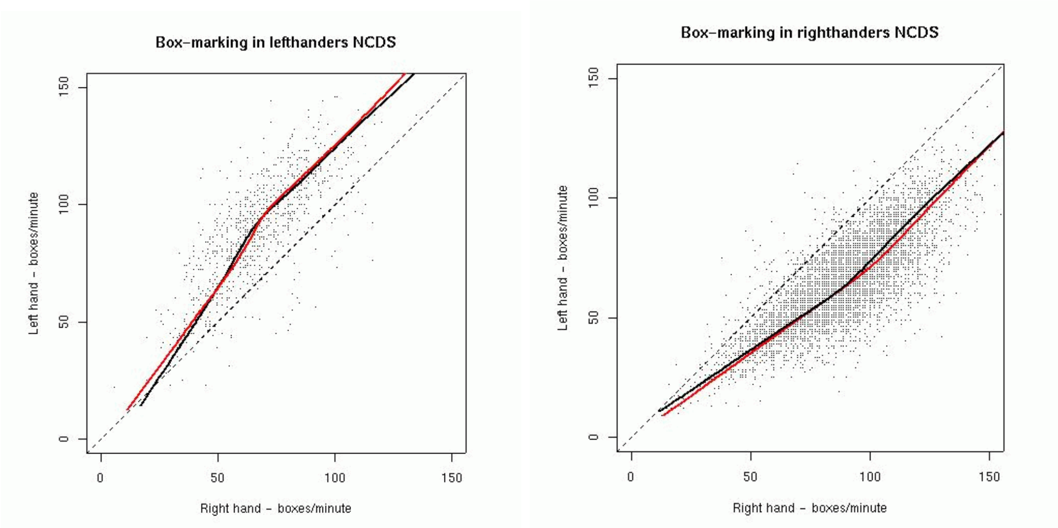


Figure 14a: Right hand versus left hand performance, in lefthanders & righthanders, on the box-marking task in the NCDS. Black = males, red = females

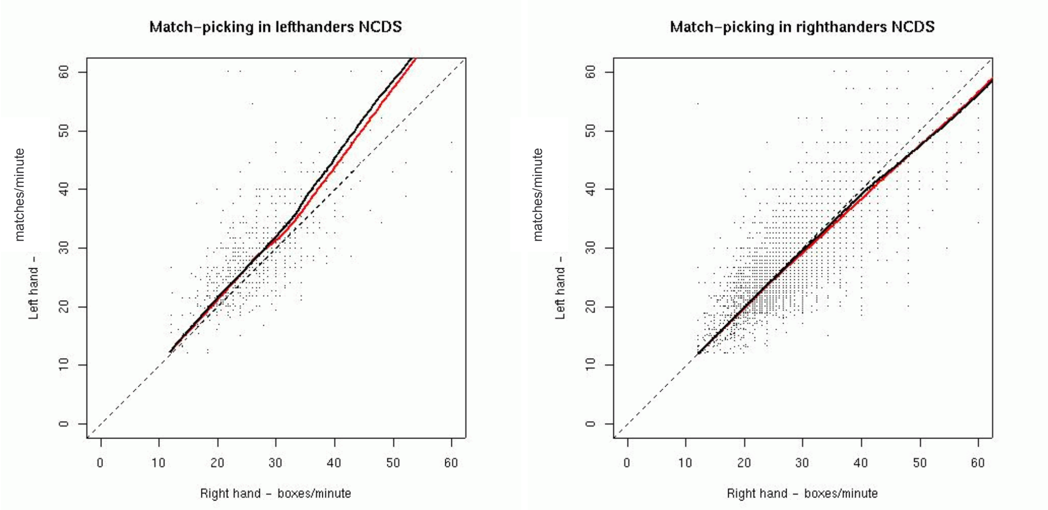


Figure 14b: Right hand versus left hand performance, in lefthanders & righthanders, match-picking task in the NCDS. Black = males, red = females

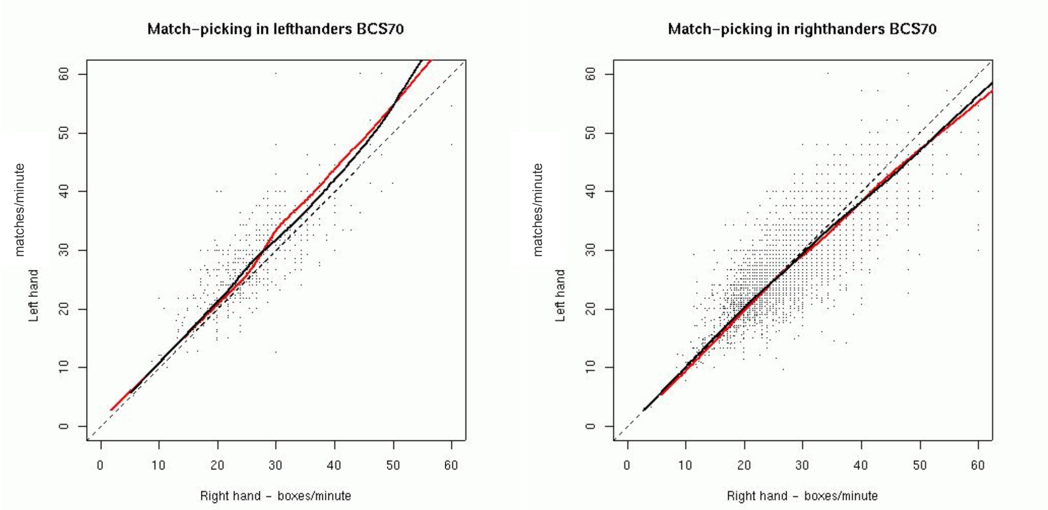


Figure 14c: Right hand versus left hand performance, in lefthanders & righthanders, match-picking task in the BCS70. Black = males, red = females

See figure 14. In summary:

- Box-marking skill - NCDS (figure 14a):
Performance at the lower ranges approaches symmetry, but rises to a maximum preferred hand superiority at about the population mean values of hand skill. This superiority is then sustained (but doesn't increase) up to the highest values. This is regardless of which is the preferred hand.

The point of inflection is around the mean population value of hand skill:
- 92/min right hand and 67/min left hand in righthanders
- 69/min right hand 91/min left hand in lefthanders.

- Match-picking skill - NCDS (figure 14b):
Hand skill remains pretty much equal from low performance to high performance, although the preferred hand does show increasing superiority for performances over the population mean. Male lefthanders show a small increase in skill difference compared to females for higher values.

- Match-picking skill - BCS70 (figure 14c):
Pretty much identical to NCDS match-picking, except that the (small) sex difference in lefthanders is reversed.

Discussion

Box-marking shows an expected lack of asymmetry for low-performers (cf. McManus' 'symmetrical handicapped' group), which gradually rises up to a fixed level of about 30% difference in performance between the hands.

Match-picking does show some advantage to the preferred hand, but this is never more than about 5% of total performance. It is less easy to interpret the increases, as they are occuring towards extremes of the plots, where numbers of cases are falling off and uncertainty is rising.

The sex-difference is small, only present in the smaller (and therefore less certain) lefthander group, and inconsistent between the cohorts, suggesting it is not significant.

Thus in box-ticking there is an apparent 'ceiling effect' in absolute skill difference. An argument about practice effects would suggest that less able individuals are getting in less practice, more able, more, and the difference is a product of practice. Match-picking tells us generally less - as suggested by the laterality indices, the differences are small. However, there is still some suggestion that the more skill one has, the greater the difference between the hands overall.

Conclusions

The two gradients seen either side of the point of inflection are intriguing.

However, while we can <u>see</u> the relationship between hand skill in these figures, it is still up to us to decide how to define the 'laterality' we're looking at.

- If laterality 'is' absolute difference, there is a ceiling effect; population preferred-hand superiority limits to about 30%.
- If laterality 'is' is a relative difference, preferred hand superiority rises to a maximum, then falls off towards the higher-performing end of the R=L line.

It should be noted that any theoretical process that can account for one conceptualisation of this distribution, can therefore account for the other as well. The only difference between 'ceiling effect' findings and 'maximum at the mid-point' findings is how laterality is conceptualised. If any hypothesis is to be testable, it is essential to be clear from the outset which conceptual model is being used. Otherwise, the danger is that almost any result could be considered 'consistent' with the hypothesis.

2b. Outcomes and bivariate measures of hand skill

- Cognitive function vs. hand performance in three dimensions

The presentation of sided difference on these measures as a 2-D plane made it all but inevitable that investigation of the relationship of this plane with respect to other outcomes should extend into three-dimensional space. The prospect of examining tens of thousands of individual observations is now an exploratory tool available on the desktop of an average PC.
This would allow for exploration of the relationships between outcome variables and hand skill without recourse to laterality indices. It would therefore allow one to see outcomes in relation not only to differences by side, but also differences in hand skill performance. Thus one can have a view of the relationships free of the mathematical and conceptual distortions that come with laterality indices. Differences by side are bivariate, and this method will give a direct view of outcomes with respect to a bivariate measure.

Methods

- Further problems in data visualisation

The only difference between a 3D plot, and the earlier 2D smoothed plots of cognitive function versus laterality index, is that the laterality axis is replaced by a two-dimensional plane of raw performance. Thus one is comparing real measures, with a similar underlying conceptual framework ie. of performance at a task.

This data can be presented as scatterplots, contour maps or grids. All these methods have problems:
- It can be difficult to appreciate spatial relationships in a 2D projection of a 3D scatterplot, especially if data is irregularly-distributed (figure 15).
- A contour map presupposes that all one is interested in is absolute height. While this is part of the picture, a three-dimensional relationship is just that, and whether one can 'see' a peak in the distance over a nearer ridge is never too obvious from the contours. Contours can of course clarify relationships in other areas.
- A 3D grid (available from many statistics packages) is also deceptive in that it extends from zero to the X & Y limits - the grid is a square (or rectangle) with bumps in it. In the case of the R and L hand performance, there is no (or little) data in the corners, but grids are usually interpolated to the edges. They do not tell you about the point density ie. the certainty with which a mean value on Z is being estimated. It remains unclear what one should take note of, and what one should ignore (see figure 16).

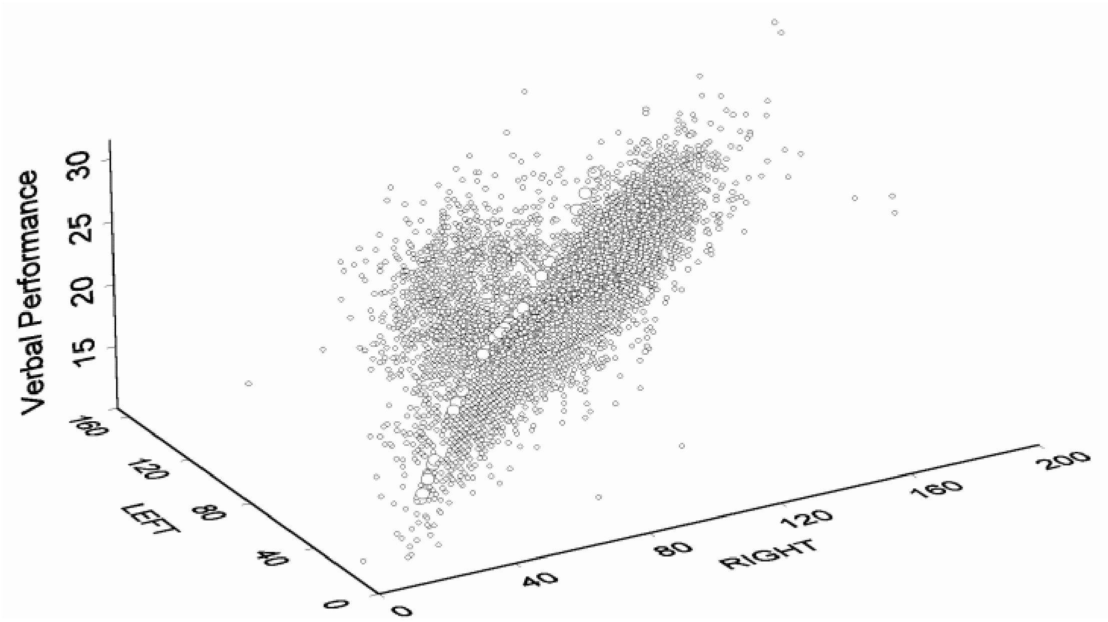


Figure 15: Plot of mean verbal performance against hand skill
- appreciating the 3D shape of these irregularly-distributed points is not easy

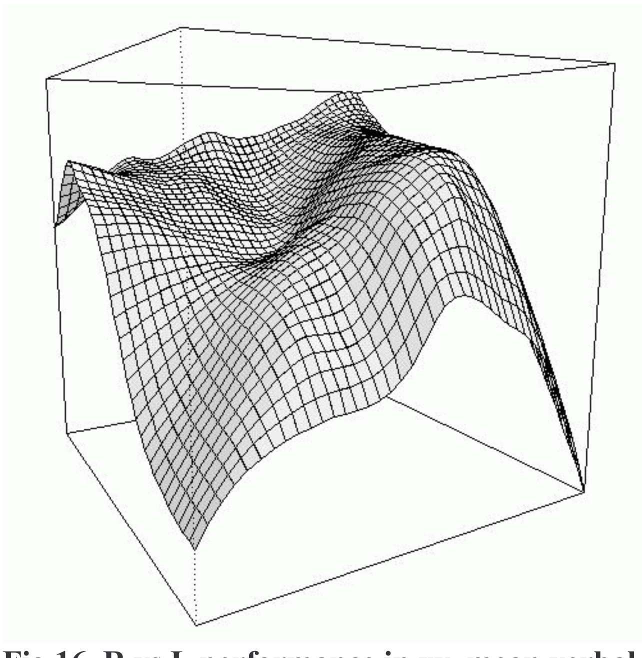
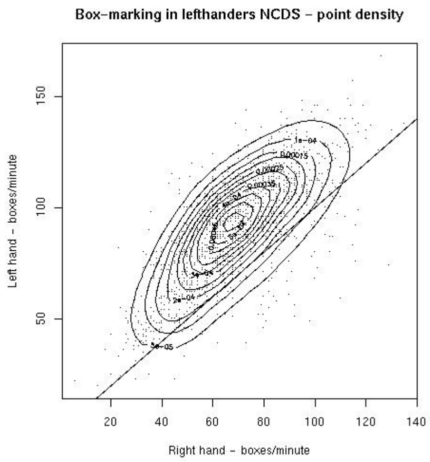
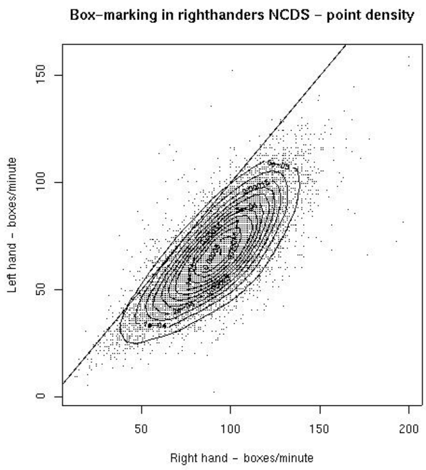


Fig 16. R vs L performance in xy, mean verbal skill on Z. Uncensored.
- Note how one's eye is drawn to the plunging, artefactual, data-sparse (or even data-free!) 'hillsides' at the corners, rather than the data-rich 'valley' at the centre

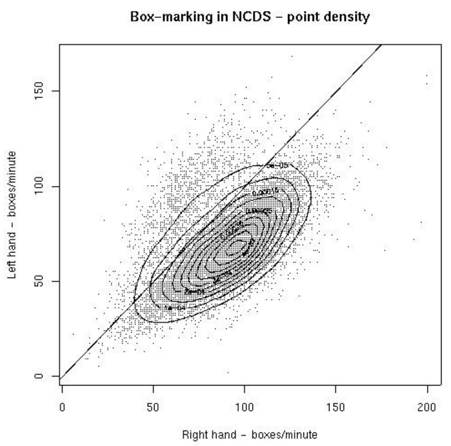
Consequently, a further stage was added. The 2D right hand performance versus left hand performance plane was examined for datapoint density - as a whole, and by handedness group (Figure 17abc). This can be seen as providing a 'cut-off' for any analyses (Figure 17d), such that where there aren't any datapoints, estimates of mean cognitive score are ignored. Subsequent figures of mean cognitive measures were then restricted to the area where the absolute point density exceeded 0.00001, a 'floor' value. This results in a figure that only exists where there is data.



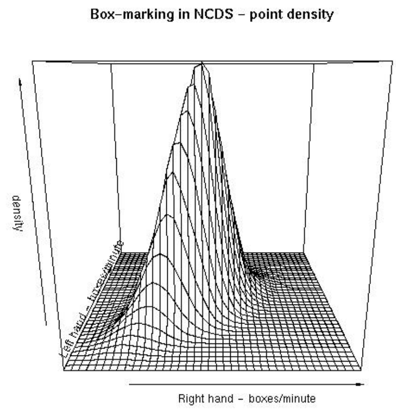
17a



17b



17c



17d

Figure 17 - local density contour maps for hand skill data. (Righthanders + Lefthanders).

Subsequent figures can then be censored, so as not to extend beyond where there is data ie. figures lie within the 'mountain' of data in 16d.

The point-cloud data produced was still difficult to visualise given the uneven scatter of points (especially on the leftside - figure 18). However, now it was established that any part of the visible figure was 'significant', the mean cognitive skill could be projected on a uniform grid of the same xy dimensions, which helped somewhat (figure 19). The non-uniform edges still made appreciating the surface's relief a challenge. By converting the cloud of points into a 3D grid, it became possible to present the figures with as many depth cues as possible, including light sources, reflection, even translucent reference planes, even as standalone 3D figures that could be manipulated on any computer with a simple viewing program. Examples of this same figure can be seen with gridlines (figure 20) and without (figure 21). An additional pair of plots of the points making up the surface, of verbal skill against right hand skill and, separately, left hand skill (figure 21), can then be used to both orientate oneself on the 3D figure, as well as providing quantitative information about the relationships.

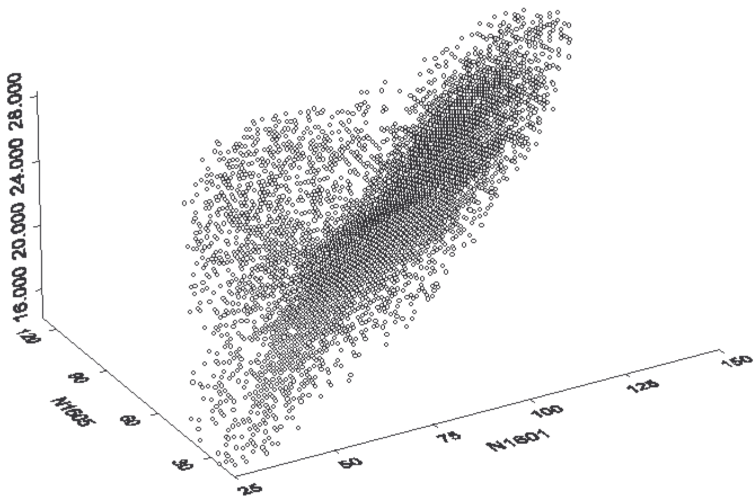


Figure 18: Mean verbal skill vs R&L hand skill - censored to areas with reasonable data density

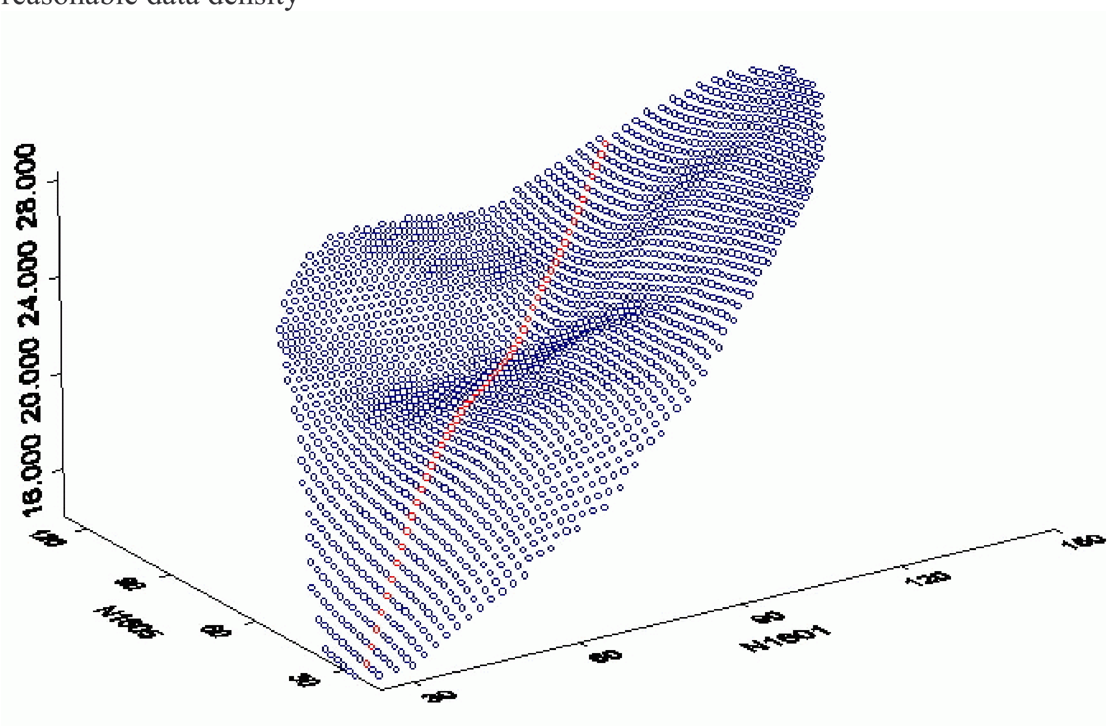


Figure 19: As figure 18, only mean IQ estimates projected onto uniform, censored grid

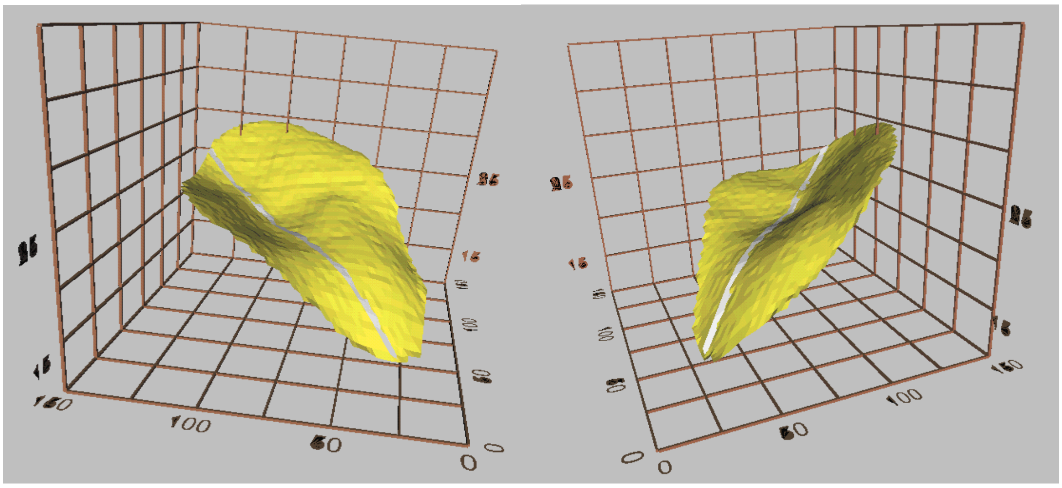


Figure 20: As figure 19, as VRML object with axes

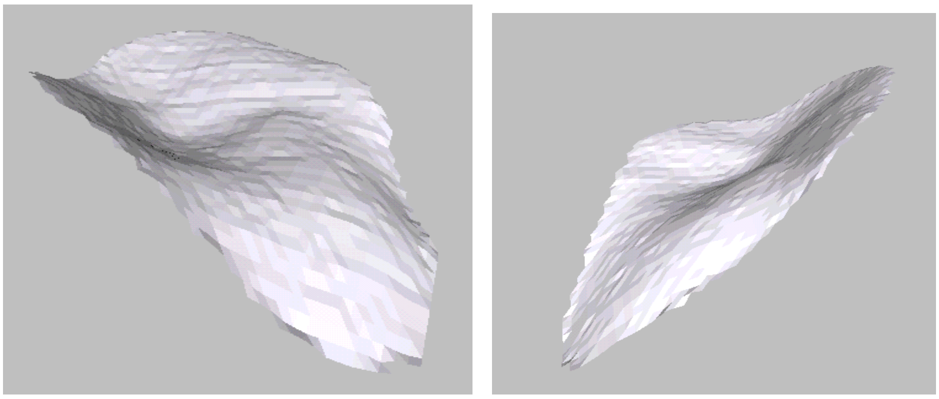


Figure 21: As figure 20, VRML object without axes

Where comparisons were made between verbal & non-verbal performance, the measures were standardised first. Examination of sex-differences was avoided, in the interests of keeping the total number of figures to a manageable level. Assessment of the 'significance' of gradient differences between different parts of the surface, while possible, was not performed, in the absence of any clear hypothesis under test.

Producing 3D figures.

Outliers were removed after detection using bivariate plots of hand skill, and derived variables (eg. 'matches picked per minute') were generated. Then the 'locfit' library was used to generate local density estimates, and local mean IQ estimates for points on the R&L hand skill plane. These were then projected onto a uniform grid, censored at the edges to remove areas of low data density (ie. where there wasn't any data). This grid was then either plotted directly, or converted into a polygon mesh (by 'QuikGrid' tm) for visualisation either using the VRweb viewer on a PC, or in Truespace 3SE for the rebuilding of axis lines etc. Final models were then carefully compared with original scatterplots to ensure the data had not been distorted or translated from true values during this process.

All the 3D figures and a suitable viewer are appended on an a CDROM disk that accompanies this manuscript. Readers are encouraged to examine these figures in three dimensions for themselves.

Results

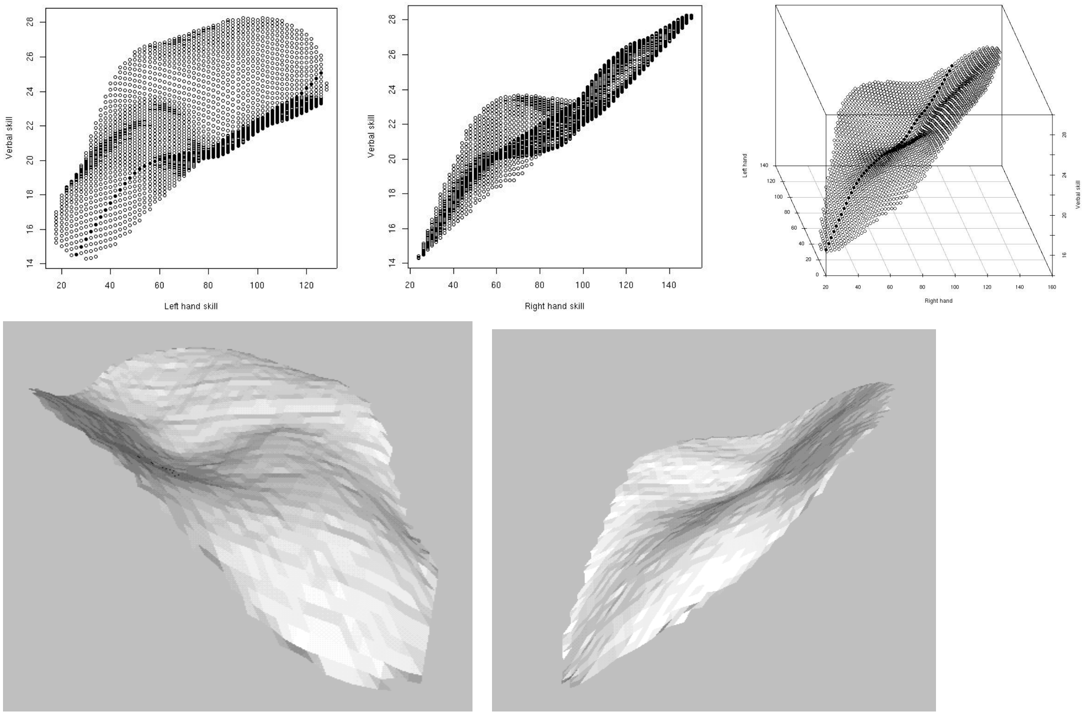


Figure 22: 3 plots of IQ vs hand skill projected against the righthand and lefthand plane, and in 3D. Dark dots mark the midline.

- Verbal skill vs. box-marking - NCDS (figure 22)

Total deviation of cognitive skill across plots:
- for verbal test, 10 (25% of scale of 40)
- for non-verbal test, 5 (12.5% of scale of 40)

The results of verbal and non-verbal ability versus box-marking can be seen (figures 18 - 22). The figure is a curved sheet with a depression in the middle. The R=L line runs like a river up a valley.
- The valley extends up and down the length (along R=L) of the figure (figure 23).
- The extremes of right & left-superiority are associated with increasing verbal skill, with the exception of the lower reaches of right-superiority, where there is a downturn.

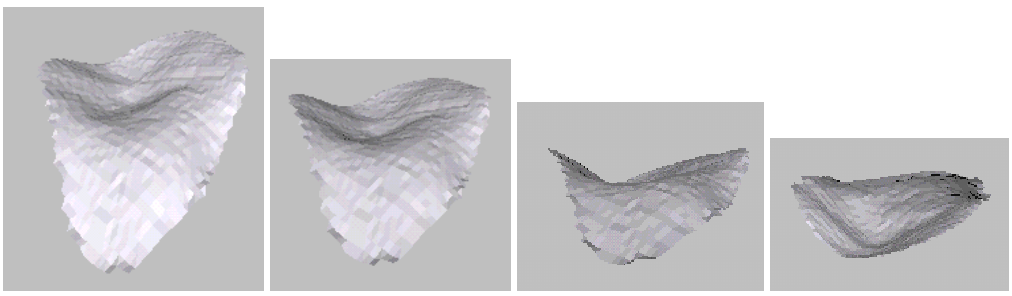


Figure 23: - Figure tipping back
- the 'valley' is sustained into tip

The sex difference in verbal skill is sustained over most of the surface apart from in the midrange hand skill at extreme left-superiority (figure 24).

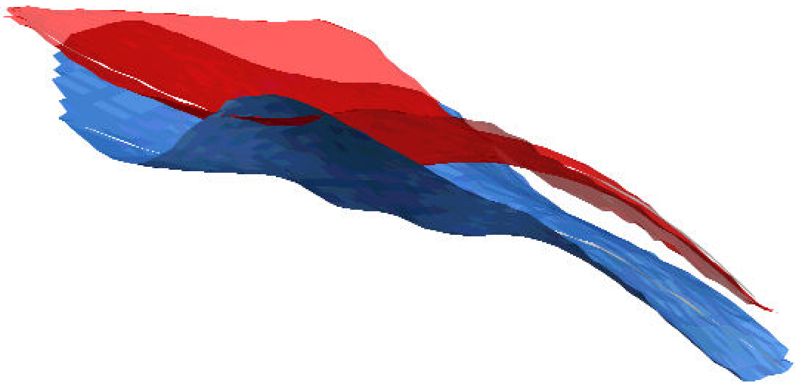


Figure 24: Sex difference in verbal ability (red=females, blue=males)

- Verbal vs. box-marking - NCDS - righthanders and lefthanders (figures 25 & 26): Dividing by writing hand, again there is a downturn in performance for extremes of right-superiority for poor-performers, but not for high-performers. One can also see that most of the variance is due to changes in skill of the preferred hand, in each handedness group ie. changes in verbal skill vary with right hand skill in righthanders and left hand skill in lefthanders.

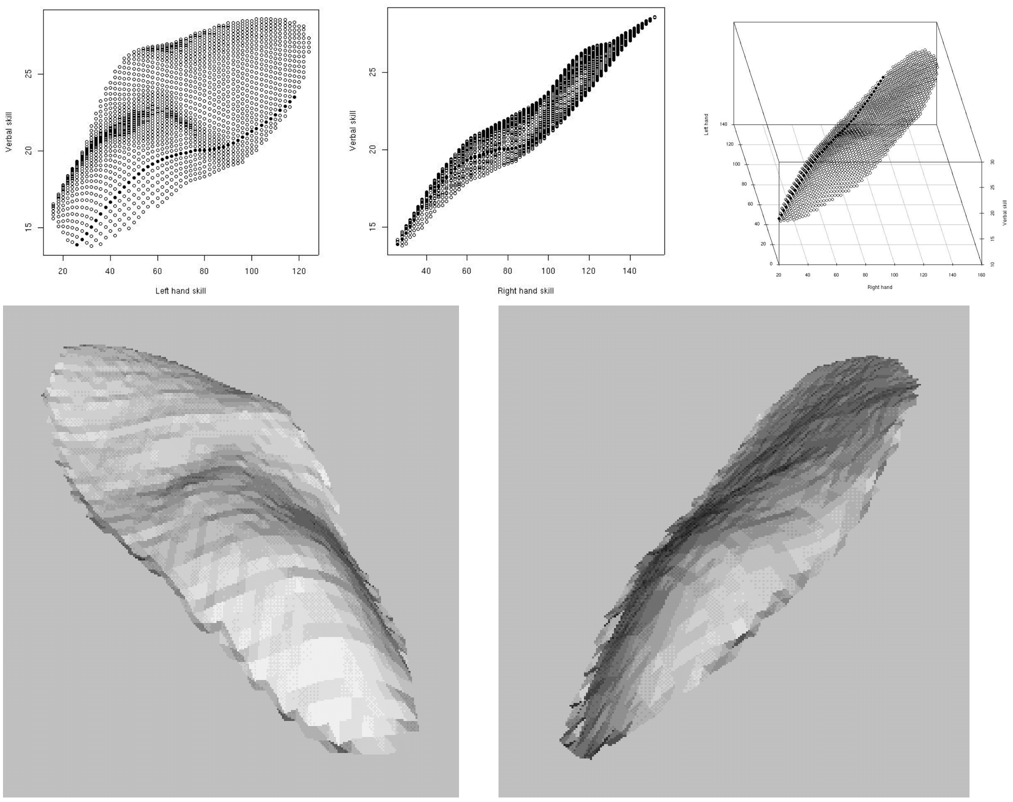


Figure 25: Verbal vs. box-marking in righthanders - NCDS

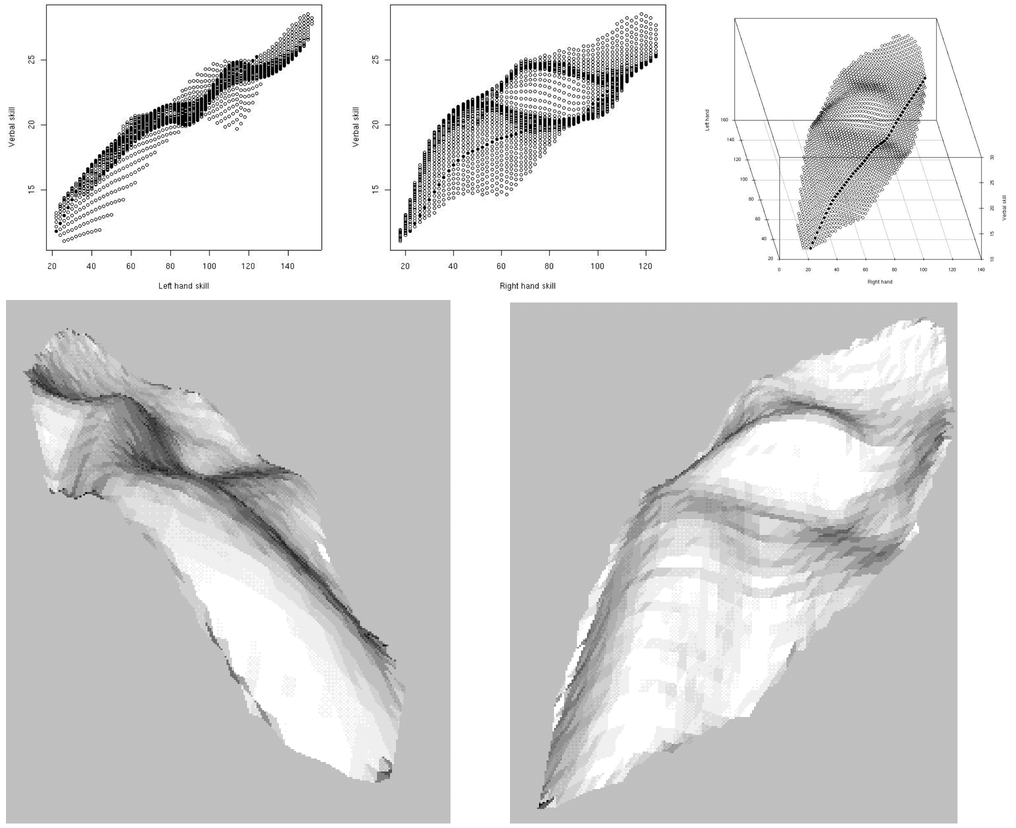


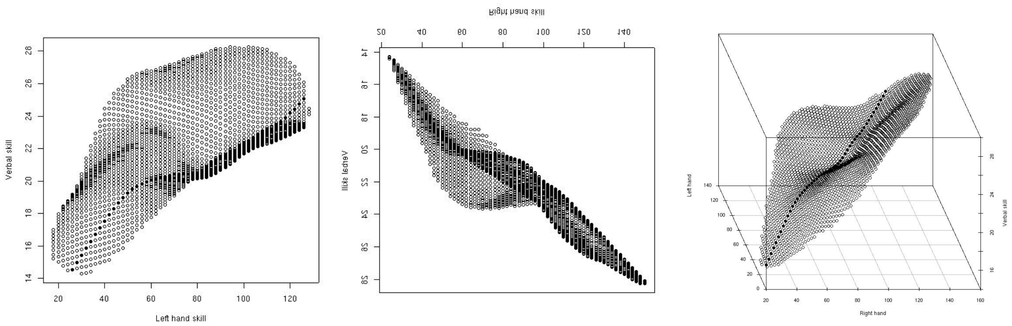
Figure 26: Verbal vs. box-marking in lefthanders - NCDS

Non-verbal skill compared (figure 27 & 28):
For non-verbal skill vs. box-marking, the figure is very similar, reflecting a high correlation between the two measures of cognitive function, which is being maintained in 'hand skill space'. To compare verbal and non-verbal skills, surfaces of mean standardised skill from both tests were plotted on a single figure (Figure 28).

The two surfaces are close throughout, but it can be seen that verbal skill is superior at all extremes except mid-range left & right superiority. Dividing by writing hand verbal superiority is now seen at all extremes (of right-superiority, left-superiority, overall highest & lowest performance). The small extension of the lefthander population provided for in a lefthander-only plot has allowed for visualisation of the maintenance of verbal superiority along the entire lefthand border.

The exception remains the maintenance of non-verbal superiority on the right, around the point where extreme right-superiority is associated with a fall-off in cognitive performance (the 'Annett homozygote disadvantage region', so to speak).

This is not merely a 'flatter' response, a lower correlation between non-verbal skill and hand skill, as this would not result in the speech-superiority towards the origin.



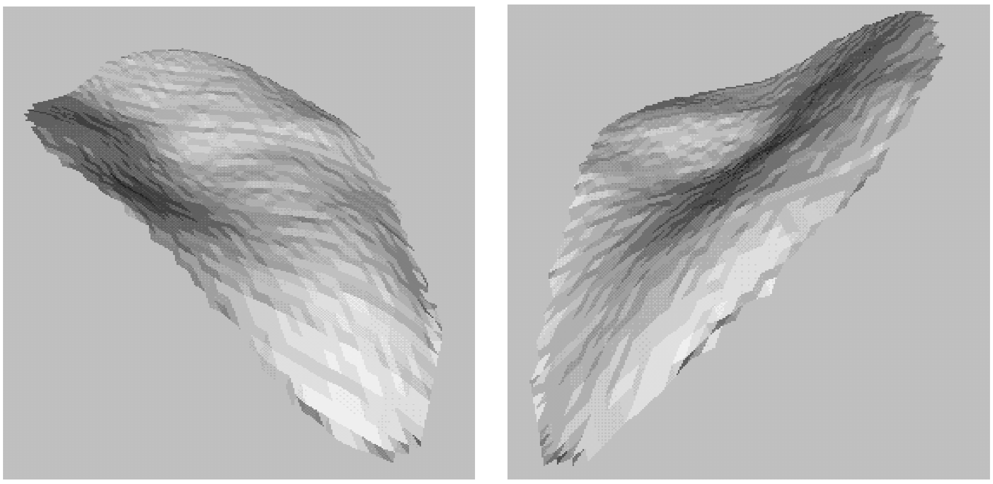


Figure 27: Non-verbal skill vs R&L hand - boxticking NCDS

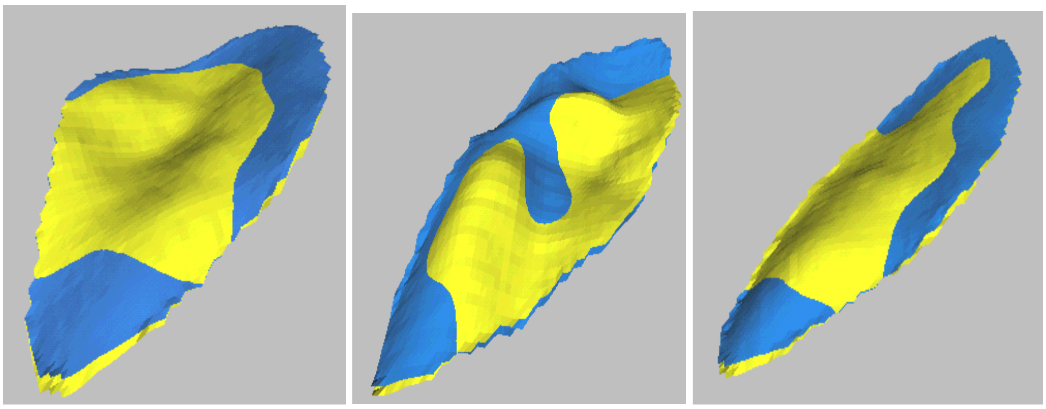


Figure 28 : Standardised verbal skill (blue) and non-verbal skill (yellow)
Verbal skill surrounds non-verbal skill in all (first figure), lefthanders (second figure), and right-handers (third figure). The separation of these two surfaces is small.

Verbal & Nonverbal vs matchpicking skill - NCDS (fig 29-31):

Total deviation of cognitive skill across plots:
- for verbal test, 6 (15% of scale of 40)
- for non-verbal test, 5 (12.5% of scale of 40)

However, once the initial 'tail' of poor performers is past, the plots are practically flat as hand skill continues to increase.

Figure 29: The figures show an initial extreme rise of verbal skill for modest improvement in hand skill, then a much more gradual increase of verbal skill for increasing hand skill. Verbal skill is maximised near the midline, although there are 'humps' of performance either side of this midline ridge for lower-middle values of hand skill.

Figure 30: Dividing by writing hand does little apart from emphasise the relief in the lefthanders. This may simply be a consequence of reduced numbers in this group.

Figure 31: Non-verbal skill is again remarkably similar to verbal skill, apart from even less suggestion of any increase in skill at higher values of hand skill.

Figure 32: Again, standardised cognitive measures are compared. These are very complex figures, of which many observations can be made.
An attempt can be made to summarise the figures as they stand, eg. "Lower-to-mid right hand superiority is non-verbal superior, upper right-hand superiority is verbal superior. Converse true across the midline."
However, as this is bordering on interpreting tea-leaves, there is perhaps more value restricting oneself to a comparison with the findings on the same measures in the other cohort, to provide some face validity at least.

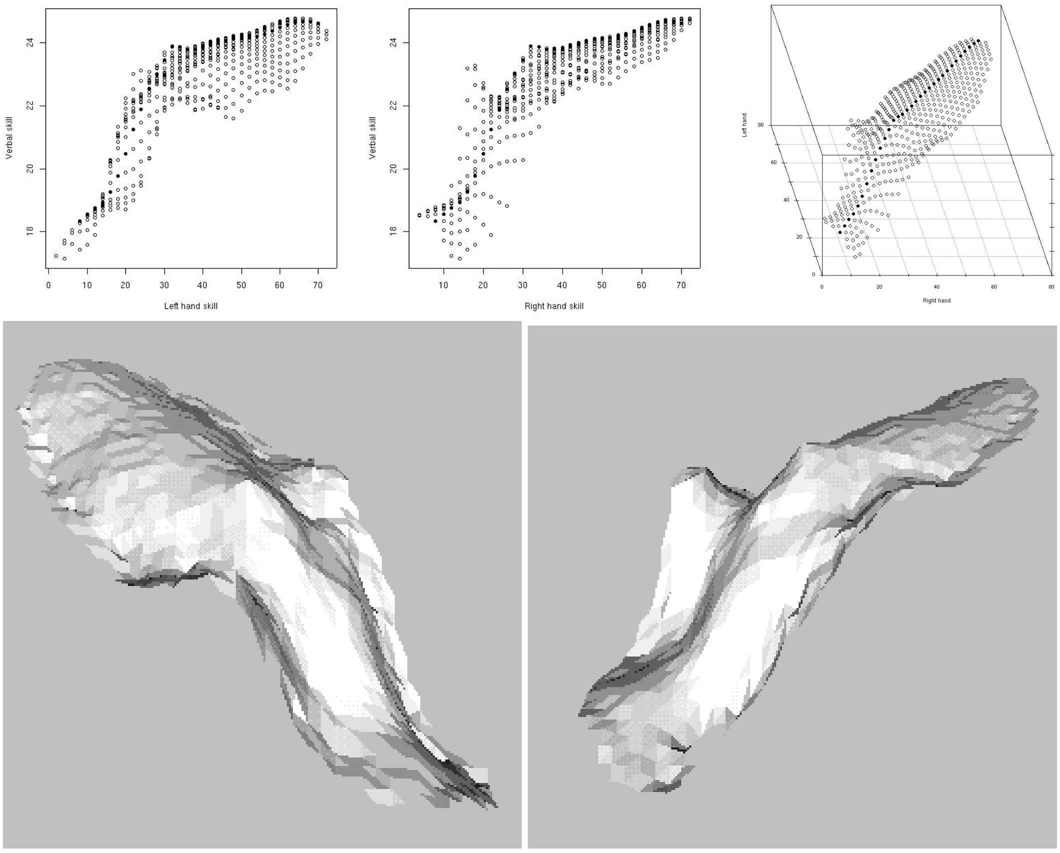


Figure 29: Verbal skill vs. match-picking task - NCDS.

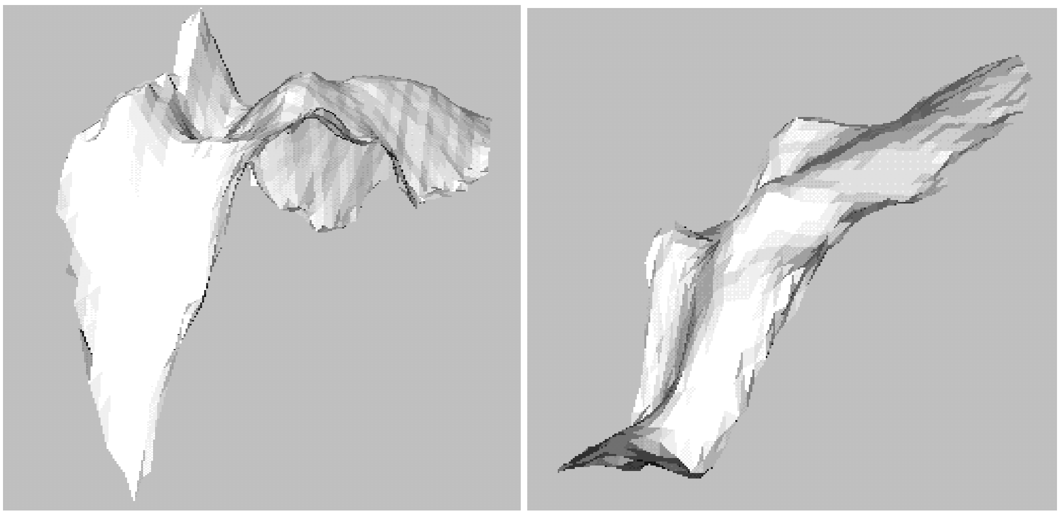
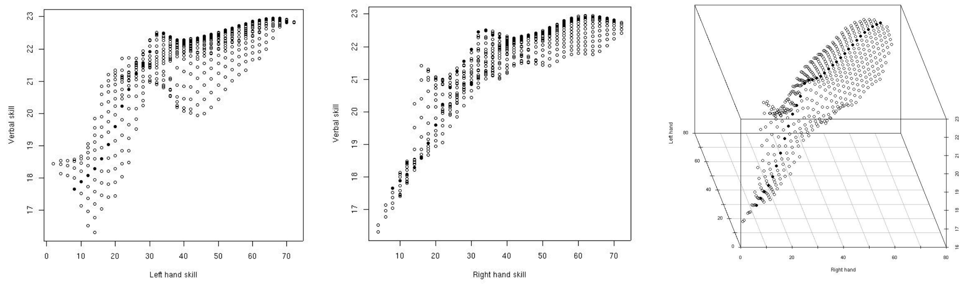


Figure 30: Verbal skill vs. match-picking in Lefthanders (on left) & Righthanders (on right) - NCDS.



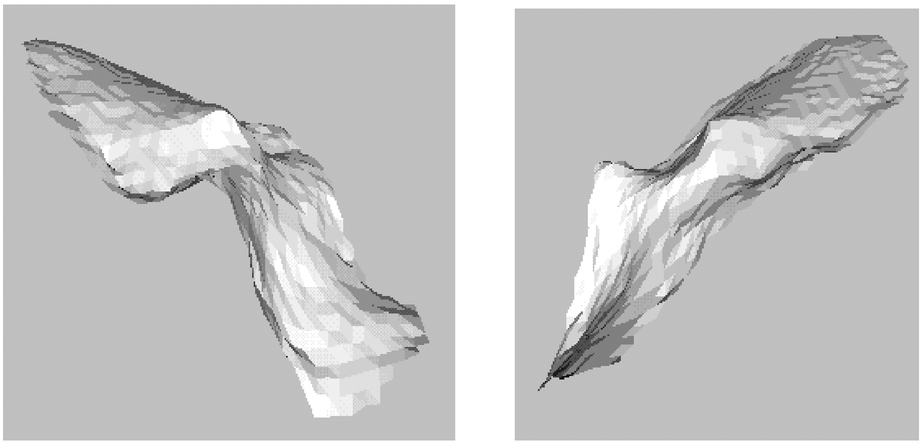


Figure31: Non-verbal skill vs match-picking - NCDS.

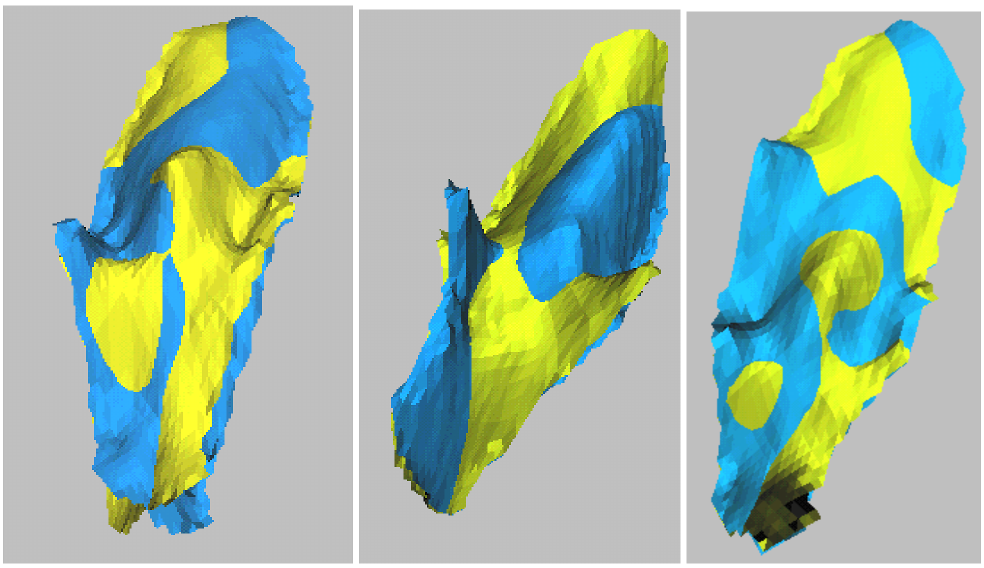


Figure 32: Verbal (blue) vs non-verbal (yellow) skill vs match-picking - NCDS.
- both hands, lefthanders & righthanders

Verbal & nonverbal matchpick surfaces - BCS70

Total deviation of cognitive skill across plots:
- verbal score varies by about 1 along the midline (2.5% of max score of 41)
- non-verbal varies by about 2 along the midline (7% of max score of 28)

As in NCDS, the majority of the variance is in the lower half of hand skill values, but in this dataset considerable variance continues into higher levels of hand skill.

Figure 33: Verbal skill once more shows a midline ridge and 'ears' either side of this ridge, around middle-rate hand skill. The fall-off towards low verbal skill is much less than in the NCDS data. Further, verbal skill actually drops off towards upper reaches of hand skill.

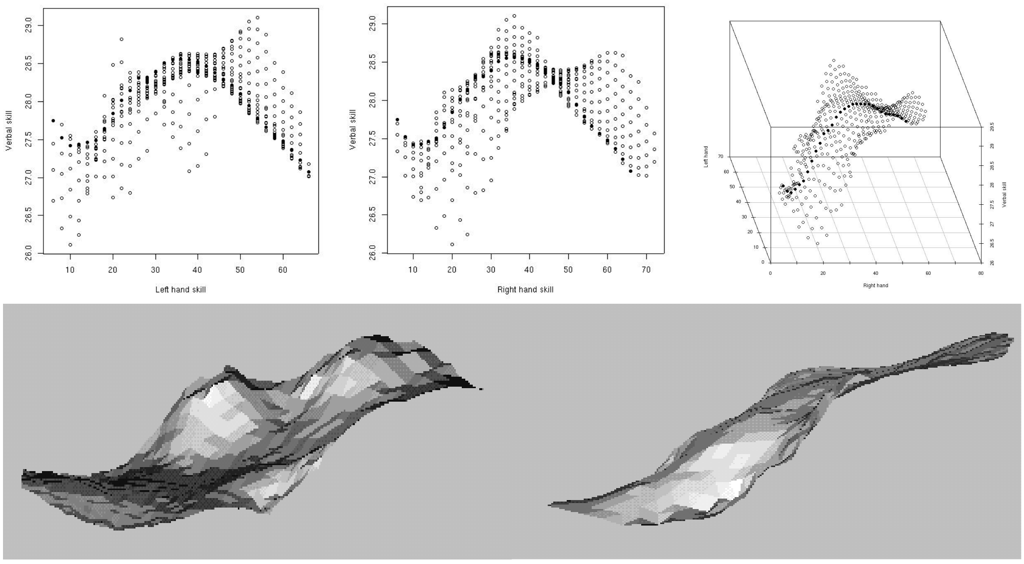


Figure 33: Verbal skill vs match-picking - BCS70.

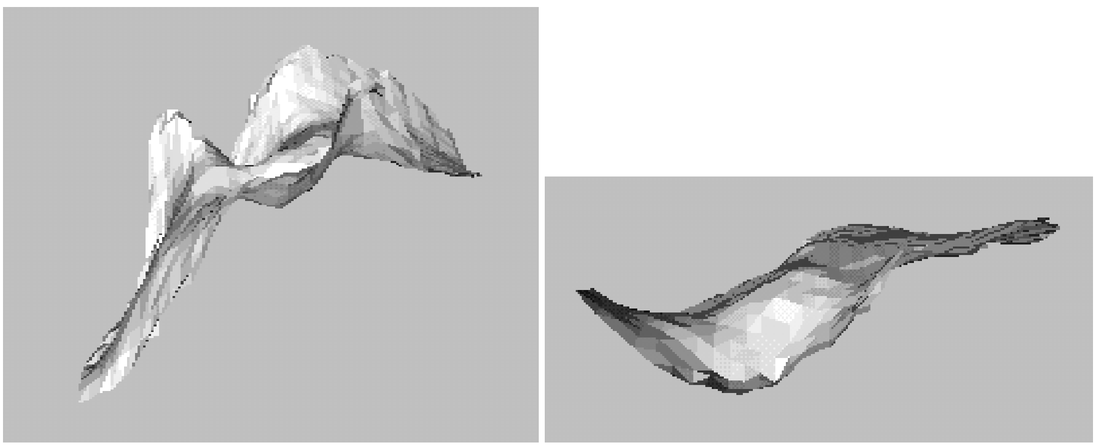
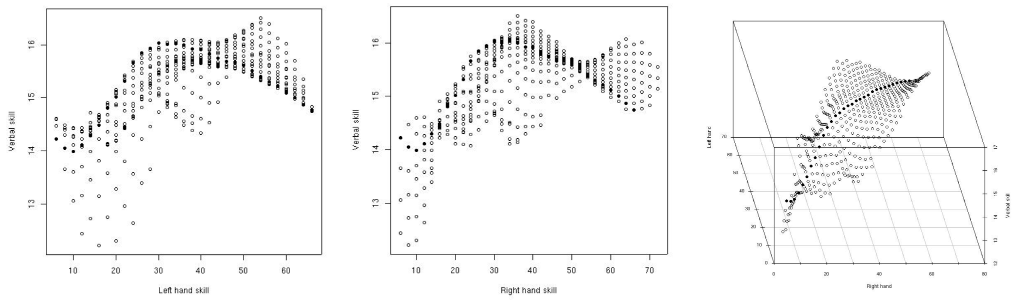


Figure 34: Verbal skill vs match-picking - Lefthanders (on left) & Righthanders (on right) - BCS70.

Dividing by preferred hand once more leads to a lefthander figure which is an exaggeration of the relief of the righthander ie. dividing by writing hand has merely given us an eleven-percent subsample, with little to suggest it hasn't been taken at random.



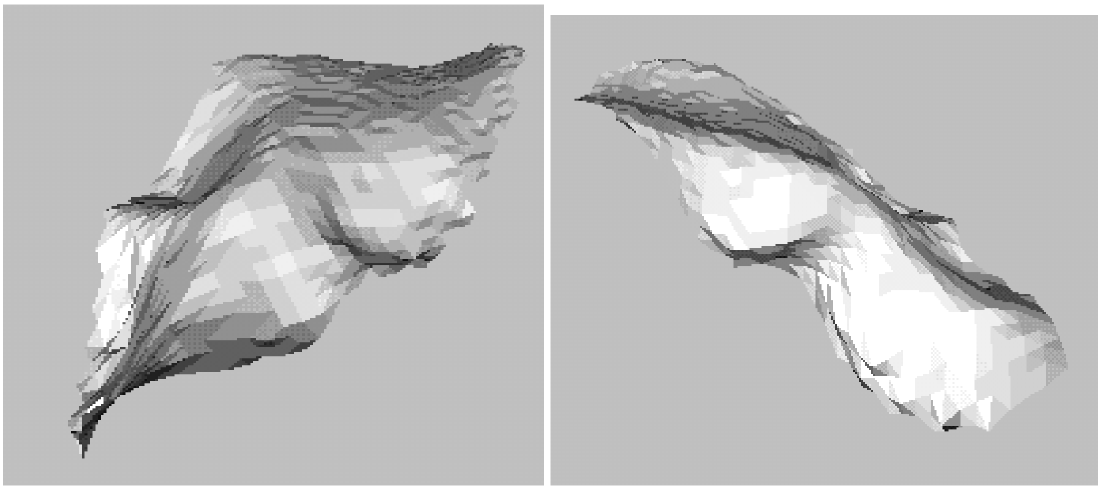


Figure 35: Non-verbal skill vs. match-picking - BCS70.
Non-verbal skill. Less suggestion of a midline ridge. Non-verbal performance falling-off towards upper values of hand skill.

Figure 36: Comparison of verbal & non-verbal skill. Again, very complex figures. Directly comparing these with Figure 30:
- From the upper end (highest hand skill) downwards, both datasets suggest bands of non-verbal superiority, then verbal, then non-verbal.
- at the centre of the figure around the midline there is non-verbal superiority in righthanders and verbal superiority in lefthanders, reversed at the edges.

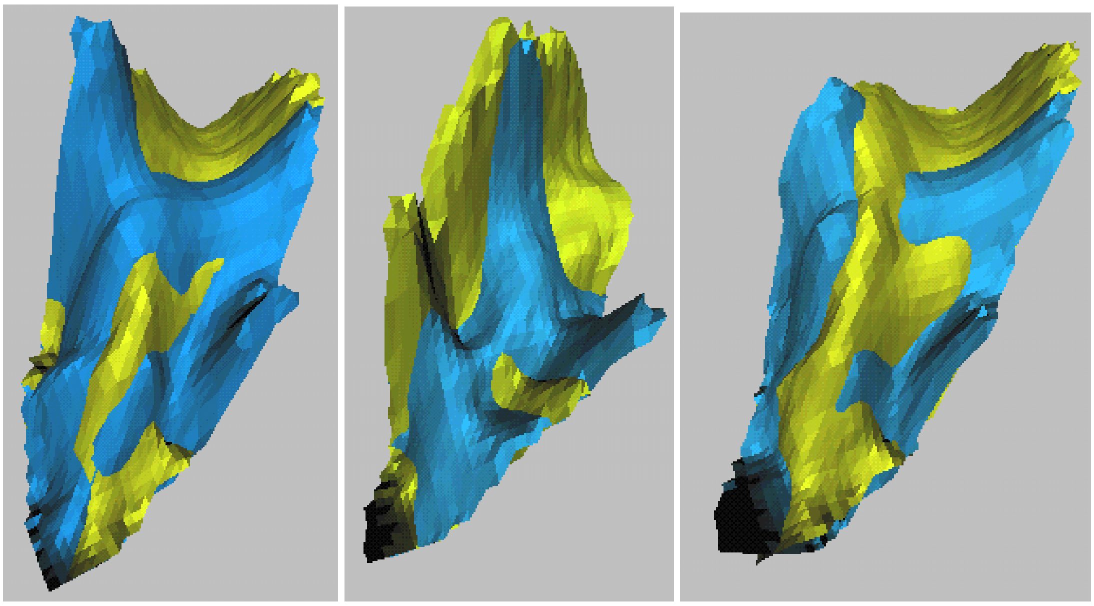


Figure 36: Verbal (blue) vs non-verbal (yellow) skill vs match-picking – BCS70.
- both hands, lefthanders & righthanders

Discussion

Thus we can now see the relationship between hand skill measures and cognitive function, free from problematic laterality indices.

Consistent, interpretable findings?
The box-marking measure leads to a remarkably consistent series of figures:
- There is a midline valley, up from the origin, followed by a flat middle section, then onwards and upwards. The 'valley walls' rise either side of this.
- There is, if anything, less of a clear valley towards the origin. This suggests that very handicapped individuals are not contributing to the valley.
- The valley continues towards high values of hand skill - handicapped groups are not causing the dip at the midline.
- Performance only falls off at extremes of right-superiority for low values of hand skill. Thus the 'heterozygote advantage', which predicts a general handicapping of cognitive function associated with extreme right-superiority, is difficult to support.

Dividing by writing hand suggests two populations, planes inclined down & in towards the midline.
- Both have a suggestion again of fall-off of cognition at extremes of hand superiority only for poorer-performers. Both show no signs of fall-off associated with extremes of hand superiority for higher-performers.
- Neither do they show any 'recovery' across the midline. Thus it would seem that dividing by writing hand is separating out two populations of performance.

The match-picking measures seem less satisfactory in several ways:
- apart from an initial catastrophic fall-off in performance, there is little relationship between hand skill and ability, which seems counter-intuitive. Indeed, for non-verbal skill there seems to be a fall-off in ability with increasing hand skill.

- the magnitude of the differences in cognitive skill across figures is small, leaving out the initial 'step up' from the origin
- there is some suggestion of a 'midline ridge' in a few figures, but it is not really present at all in others.

The topology is real, the relationships unambiguous, but they suggest little of interest beyond confirming the presence of a group of individuals handicapped in both cognitive and hand skills.

Problems with quantifying the results

Clearly one would next wish to quantify these effects. Total effect sizes can be read off the X, Y & Z-axes of the scatterplot projections for each figure. 95% confidence interval surfaces can be generated, which can give some idea of the significance of a given hump, although these are trickier still to visualise - on the whole, features away from the edges that make up more than half of the figure are significant deviations from a plane.

Conclusions

The 3D figures seem richly informative. They allow for appreciation of relationships obscured by laterality indices. They provide a readily-appreciated 'story' of how laterality and cognitive performance are related. They allow for resolution of questions that previous analyses using laterality indices could not resolve eg.
- that the over-representation of handicapped groups near the midline cannot really account for the dip at zero seen in 2D analyses, and
- that there is not evidence here of a drop in performance for all extremes of right-superiority. Indeed, what restricted dip there is can be seen for poor-performing right-superiors and left-superiors.

Comparison between laterality measures:

What is the 'fundamental' measure? There is a point at which one has to face whether a given measure is telling one something about a relationship. For reasons of consistency and effect size, box-marking seems more informative in these figures than match-picking. A measure correlating with verbal skill (arguably a unique human characteristic - see chapter 3), is also correlating with hand preference (whose distribution is also arguably a unique human characteristic - see chapter 2). Perhaps the lateralization of these measures (or the processes leading to this lateralization) are related in some way. Given the consistency and effect size, it is attractive to wonder whether what one can see, taking box-marking performance as a proxy measure of central, cerebral performance (and thereby laterality), is the relationship between cognitive processing performance versus lateralization of that processing.

Comparison between cohorts

The similarities of the findings in match-pick between the cohorts suggests there are no major differences between the subjects in the two cohorts. It could be assumed that this would also be found if BCS70 had been measured using the box-ticking task. However, they were not. The anomalous verbal skill result is a difference between the cohorts which might reflect differences in their lateralization at box-ticking, although this seems unlikely.

Thus, we have found 3D visualisation interesting and informative, if a little stultifying in match-picking. It is the only way to gain an unhindered view of the relationships between an outcome and a bivariate continuous measure. This unhindered view has shed light on a number of issues.

Chapter summary

The relationship between hand skill, cognitive function, and sided differences in hand skill is explored using laterality indices, and without laterality indices.

The relationships between cognitive function and laterality index, while interesting, remain ambiguous. The distribution of right and left-hand performance, shows a clear inflection at the midpoint of the population, although how this is interpreted depends on how laterality is conceived. The relationship between cognitive function and performance by side on the two laterality measures sheds light on a number of issues, although the box-marking task appears to correlate better than match-picking.

Chapter 9: Lateralization & adult outcomes

- A distance from the origin and the midline

Introduction

The existence of a relationship between cognitive function and laterality suggests a further question: Whatever the variation in cognition in the population associated with sided hand performance differences, is this reflected by real differences in social or psychological outcome? Or is it, in practice, merely a curiosity?

Findings related to ability are often immediately promoted to the status of findings related to 'selective fitness', without any real evidence that increased fitness follows. In this cohort data, however, we have the chance to explore whether there is any noticeable influence of the sided differences on outcome. Without any impact on outcome, relationships with cognitive function would lose much of their impact; whatever the differences by side may be, it is not affecting outcome.

What follows is an examination of
- social outcomes, and
- psychiatric outcomes
with respect to the R vs L performance plane.

The results will primarily be compared with the findings on cognitive function from the previous chapter. We will be asking if the relationships show similarities between measures and cohorts.

Social and psychological outcomes

Ultimately, however it is being maximised, natural selection will by definition favour fecundity, a notion encompassing the average number of offspring, the rate of reproduction and the fitness of offspring. 'Success' in society is not the same as fecundity. It is impossible to say with any certainty whether the skills required to gain a university degree are related in any way to the skills that would have been required to survive well 50,000 years ago. The skills required to satisfy the upper reaches of Maslow's "Hierarchy of Needs" in the presence of the lower, are not necessarily the same as those required to guarantee the lower.

Nevertheless they may be the same skills. The concept of "Machiavellian Intelligence" assembles early evidence suggesting that the evolution of intellect was primarily driven by selection for manipulative social expertise within groups, where the most challenging problem faced by individuals was dealing with their companions (Byrne 1988). There may be a central set of skills which have always characterised individuals that get on in human societies. They may come across as 'charisma', difficult to define but rooted in social ability and communication skills.

"Success" versus lateralization

Method

'Success' measures

Variables relevant to notions of 'success' were sought in both cohort datasets. A review of possible candidate measures eventually came down to the broad headings of "education", "social class", "income" and "offspring", specific and comparable measures of these being available in both cohorts.

- Highest educational achievement (Table 1)
Again, this is influenced by many factors outside the subjects' control, such as education provision and social deprivation. It still gives some measure of the social/cognitive functioning required to proceed successfully through the tiers of education in this country.

- Social class (Table 1)
Parents' social class, while perhaps some indicator of genetic loading, is not of itself a measure that will tell us about the subject's own success. Subject's most recent social class is better, as this is something they at least have to maintain themselves. Some measure of to what extent they have managed to improve their class over that of their parents is perhaps better still ie. difference between subjects and parent's social class. Both measures will be examined.
Social class unfortunately is a fairly broad categorical measure, compared to the enormous variety of social differences that make up the notion. Nonetheless, it is a well-accepted measure of something to do with 'success' in the eyes of society.

- Income
A very variable measure, but undoubtedly the measure of the ability to ' bring home bacon' in modern society. In today's market-driven economy it could be argued that this really is the perceived worth of an individual's contribution to society (although a myriad of exceptions could be made to this). This might be in contrast to what has been valued socially in the past, or the actual skill required to perform the job involved.

- Number of children
In selection terms, number of natural children is part of the most sensitive indicator of survival fitness of all, fecundity. The other components of fecundity, rate of reproduction and fitness of offspring, are not so easily derived from the cohort data, censored as it is well below the age at which reproduction stops.

Max educational achievement:
0 - No quals
1 - CSE grade <2
2 - O-level
3 - A-level
4 - Other higher eg. nursing qualification
5 - Degree
6 - Postgraduate qualifications eg. MPhil, PhD

Social class:
0 - SC5
1 - SC4
2 - SC3(manual)
3 - SC3 (non-manual)
4 - SC2
5 - SC1

Table 1: Categories employed for 'Maximum educational achievement' and 'Social class'.

Statistics

Data distribution

The histograms of each measure can be perused (figs 1-5). Skew and bimodality in 'Max educational achievement' (fig 1) and 'Number of kids (fig 5) was not corrected, as the impact on estimates of central tendency (compared to using negative binomials, say) were small for the purposes of these figures. The skew in weekly earnings (fig 2) was satisfactorily square-root transformed closer to normality. The skew in social class distribution (fig 3) was not altered, as again transformation had little effect on central tendency in this data.

Figure scales & effect sizes

As in the previous chapter, mean outcome scores were estimated to make up 'hand skill surfaces' for each measure. A deliberate decision was made to scale axes to facilitate (qualitative) appreciation of shapes, rather than standardise them to facilitate (quantitative) appreciation of effect sizes, although comparing a given figure's X or Y vs Z-axis scatterplot with the appropriate histogram allows an appreciation of the relative magnitude of any effects.

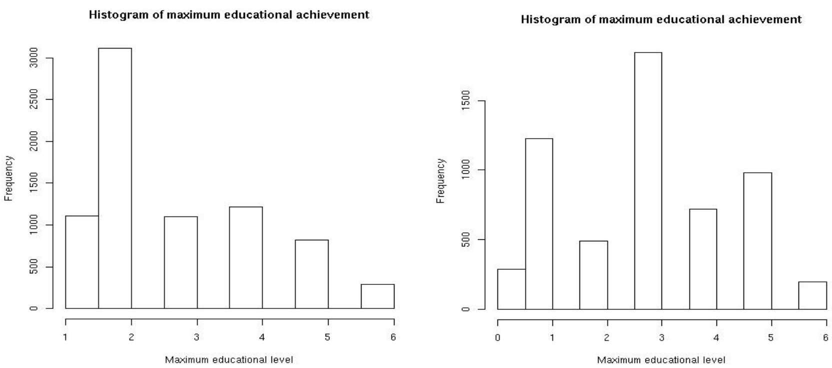
Error estimates

95% confidence interval surfaces can be generated, as mentioned previously. However, in the interests of brevity these are not included in this account, as they are of less relevance to this initial exploration, asking as it does 'are there patterns here, consistent between measures and cohorts'?

Results

Adult outcomes - NCDS - mean (sd)	Males RH	Males LH	Females RH	Females LH
Maximum eductional achievement	2.95 (1.4)	2.86 (1.3)	2.64 (1.4)	2.64 (1.4)
Social class @33	2.82 (1.2)	2.71 (1.2)	2.77 (1.2)	2.68 (1.2)
Social class change	0.53 (1.5)	0.48 (1.4)	0.53 (1.5)	0.41 (1.5)
Weekly earnings	330 (173)	321 (162)	160 (140)	148 (110)
Number of kids by 33	1.32 (1.1)	1.23 (1.1)	1.6 (1.1)	1.59 (1.1)
Adult outcomes - BCS70 - mean (sd)				
Maximum eductional achievement	2.93 (1.6)	2.88 (1.6)	2.89 (1.5)	2.95 (1.5)
Social class @26	2.58 (1.5)	2.51 (1.6)	2.87 (1.3)	3.02 (1.2)
Social class change	0.17 (1.73)	0.06 (1.8)	0.46 (1.6)	0.55 (1.5)
Weekly earnings	237 (107)	234 (123)	176 (89)	168 (78)
Number of kids by 26	0.3 (0.6)	0.24 (0.5)	0.49 (0.6)	0.32 (0.5)

Table 2: Adult outcomes in NCDS & BCS70



NCDS BCS70

Figure 1: Histogram: Max educational achievement

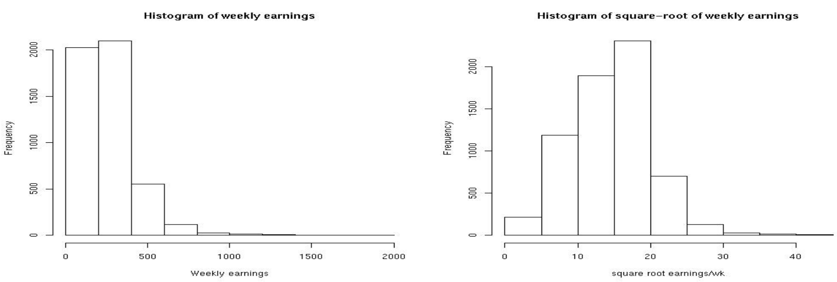


Figure 2a: Histograms: Weekly earnings, and square root (weekly earnings) - NCDS

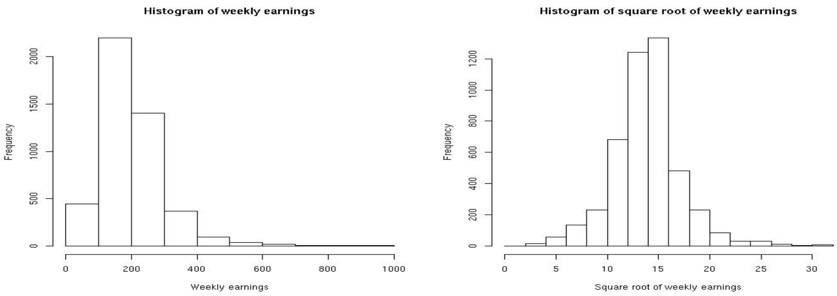
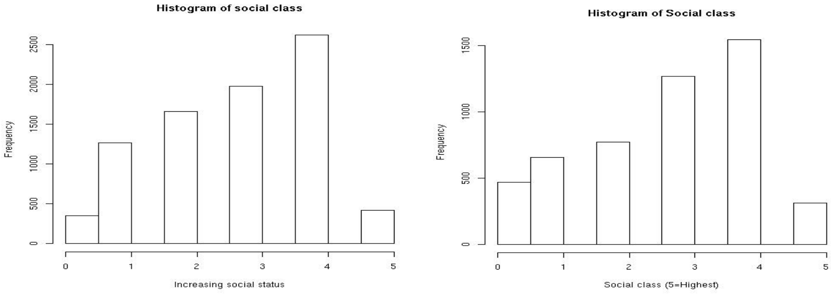
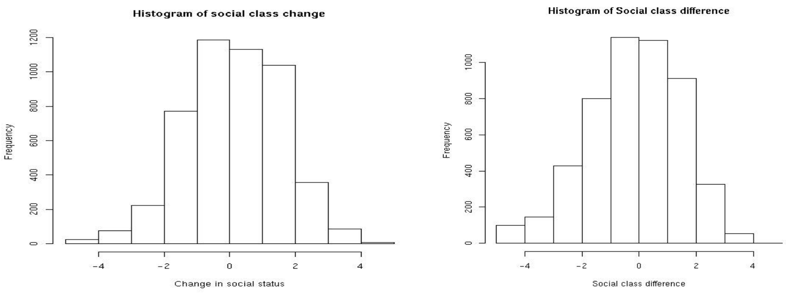


Figure 2b: Histograms: Weekly earnings, and square root (weekly earnings) - BCS70



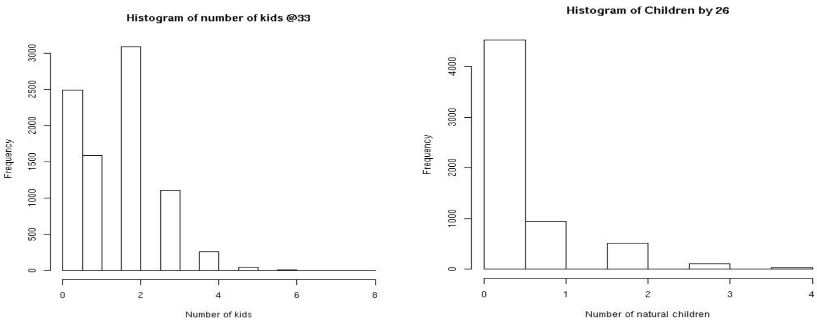
NCDS BCS70

Figure 3: Histogram: Social class distribution (highest towards the right)



NCDS (0-33yrs) BCS70 (0-26 yrs)

Figure 4: Histogram: Change in social class



NCDS - offspring by 33 BCS70 - offspring by 26

Figure 5: Histogram: Number of children

Table 1 & figures 1-5: Adult outcomes.

Broadly, the two cohorts compare well. The differences between them are best seen in the smaller 'wage gap' and closure of the 'education gap' between the sexes. The weekly earnings and number of offspring are difficult to compare, given the different ages (33 and 26) at which the measures were taken. The histograms show a huge rise in 6th-form and university attendance and social class skewing to the right (presumably largely reflecting improvements in the lot of women) in the twelve years that separate the two cohorts.

3D figures - Box-marking (NCDS)
The clearest consistency between the figures that follow is a fall-off in performance toward the origin ie. a correlation between hand skill and all of these measures of social success.

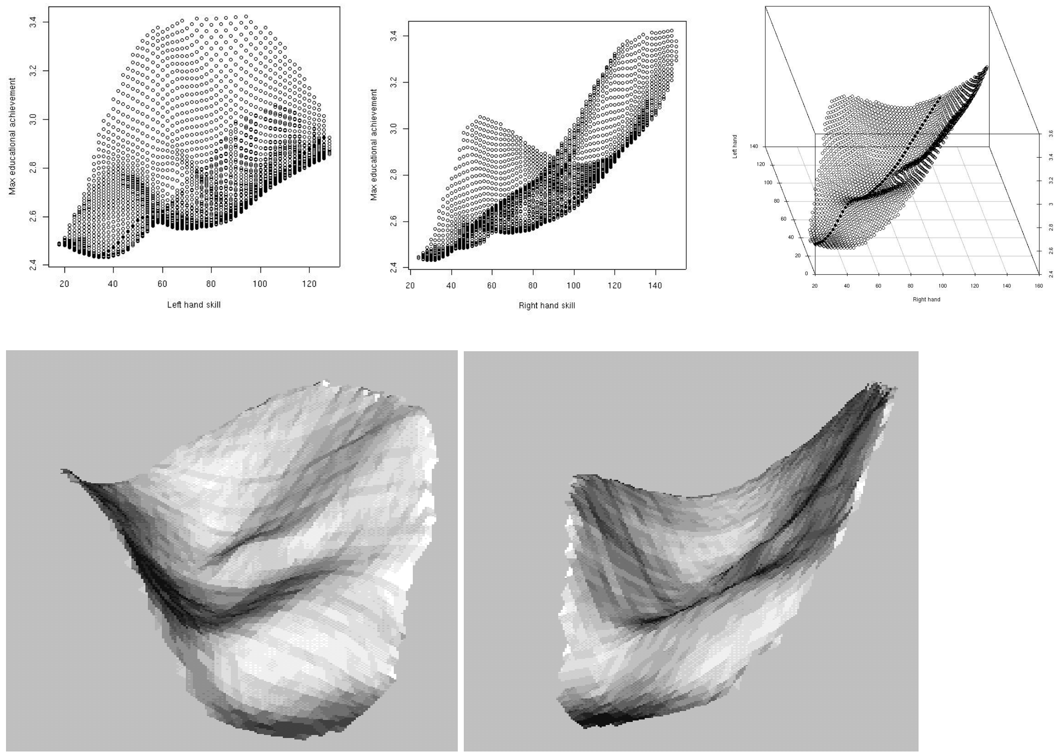


Figure 6: Maximum educational achievement vs. box-marking - NCDS
Total deviation ~ 17% of scale (~1 /6)
This is very similar in shape to the cognitive measures, with a midline valley and benefits either side of this.

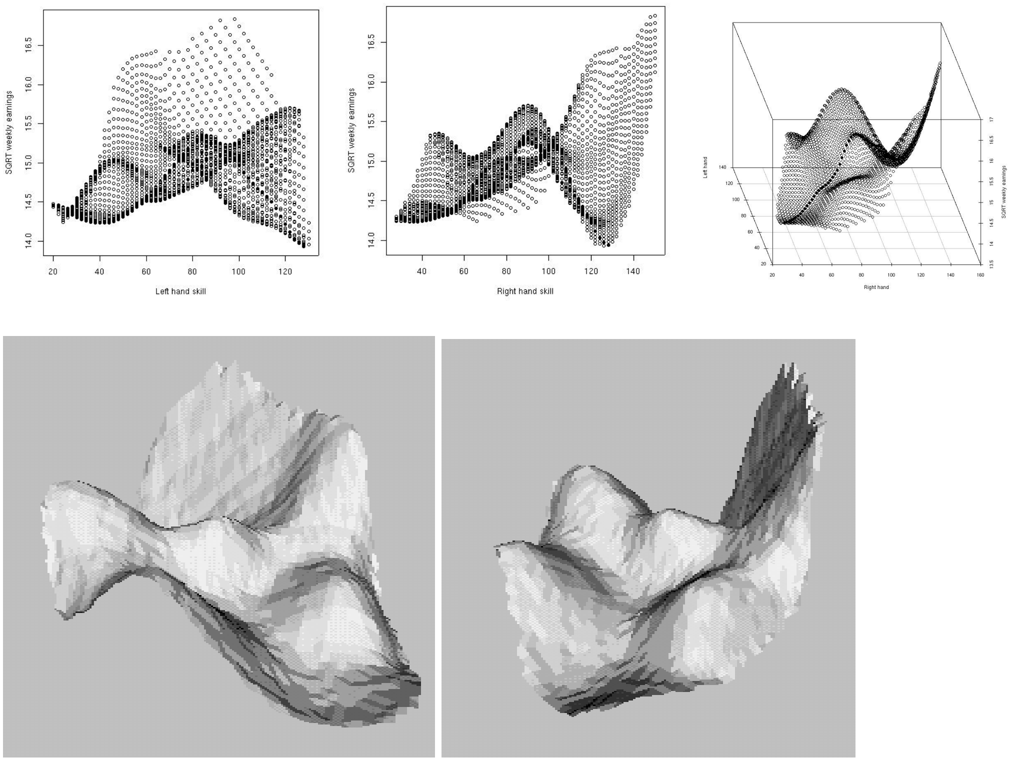


Figure 7: (square root of) Weekly earnings vs. box-marking - NCDS
Total deviation ~ 16% of scale (2½/30)
Demonstrates a midline groove, although there is a 'hump' in the middle of the distribution. Extreme high-performing righthand superiority seems well-rewarded.

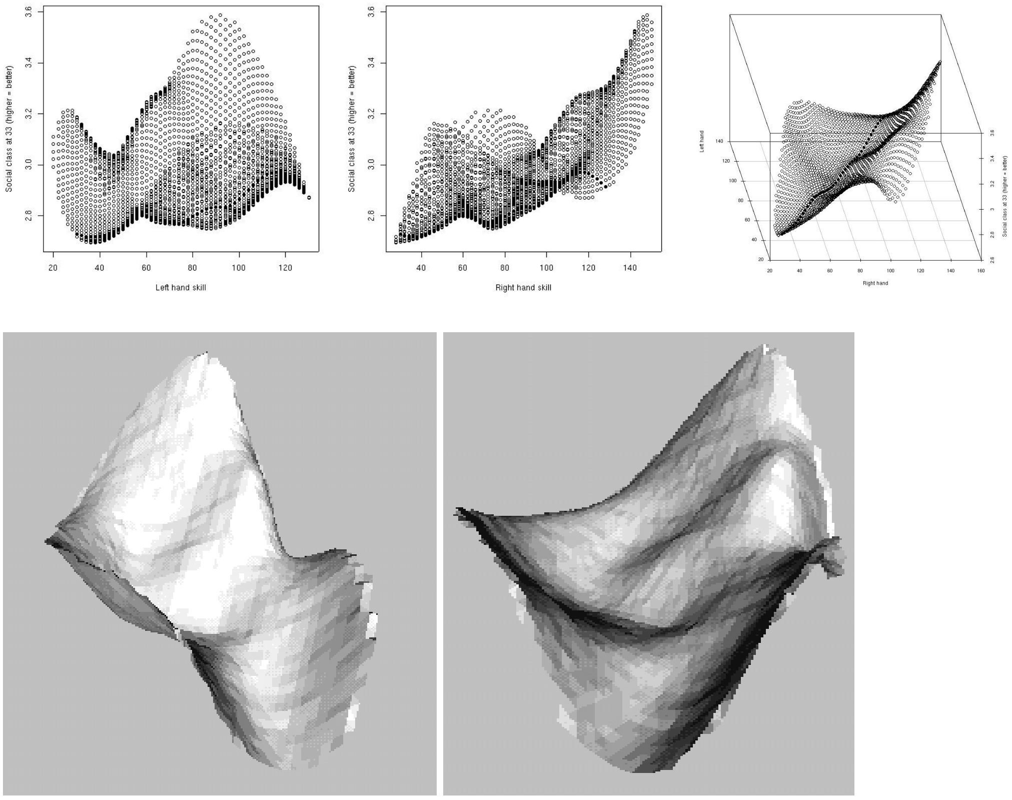


Figure 8: Social class @33 vs. box-marking - NCDS

Total deviation of midline ~ 16% of scale (0.8/5)

A midline valley, with fairly consistent fall-off at extremes of right-superiority except for the very highest-performers.

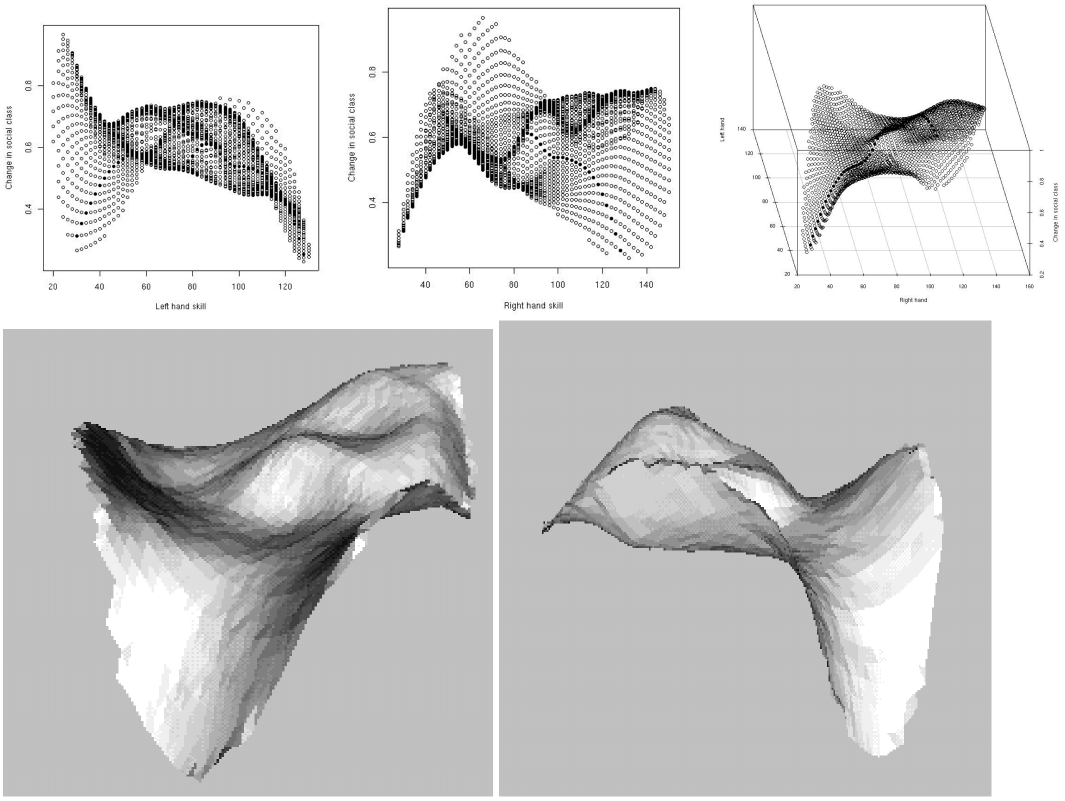


Figure 9: Social class change between birth and 33 vs. box-marking - NCDS
Total deviation of midline ~ 4% of scale (0.3/8)
The right-superiority fall-off and 'central bump' seen in earnings is again in evidence, rather than a midline valley.

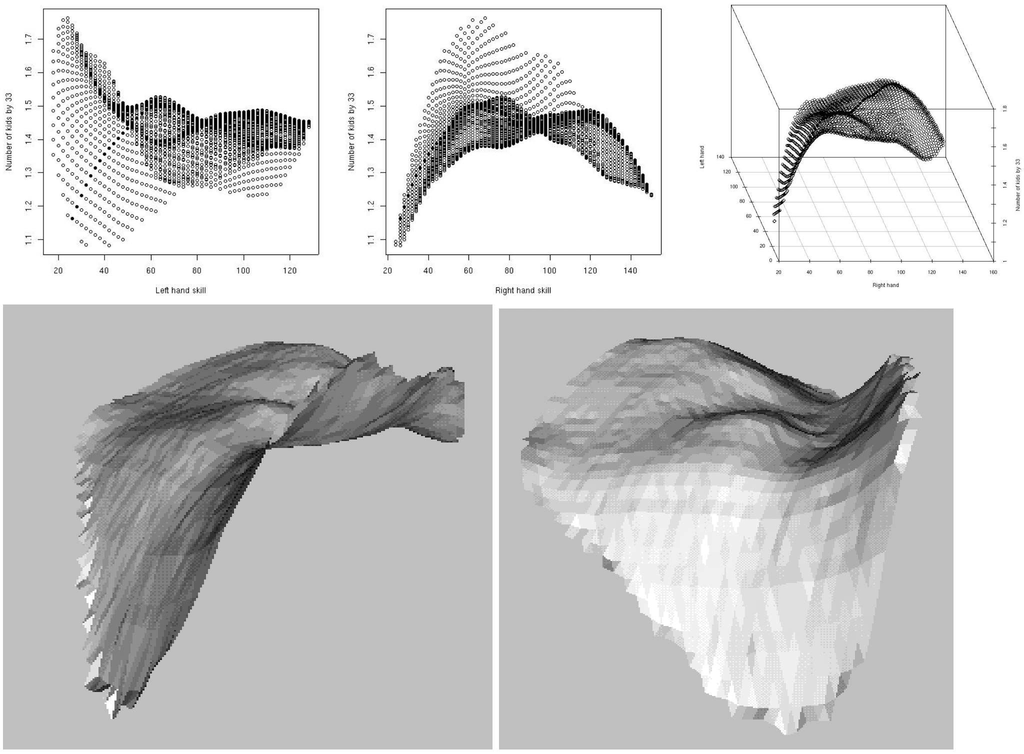


Figure 10: Number of kids by 33 vs. box-marking - NCDS
Total deviation of midline ~ 10% of scale (0.6/6)
There is a small increase ('0.3 children'(!)) for mid-range right-superiors.

3D figures - Match picking (NCDS & BCS70)
Despite the difficulties in clear interpretation encountered in the last chapter, these figures are presented as they are the only inter-cohort comparison available. Consistency between the cohorts provides a measure of face validity to any findings ie. findings generalise between populations.

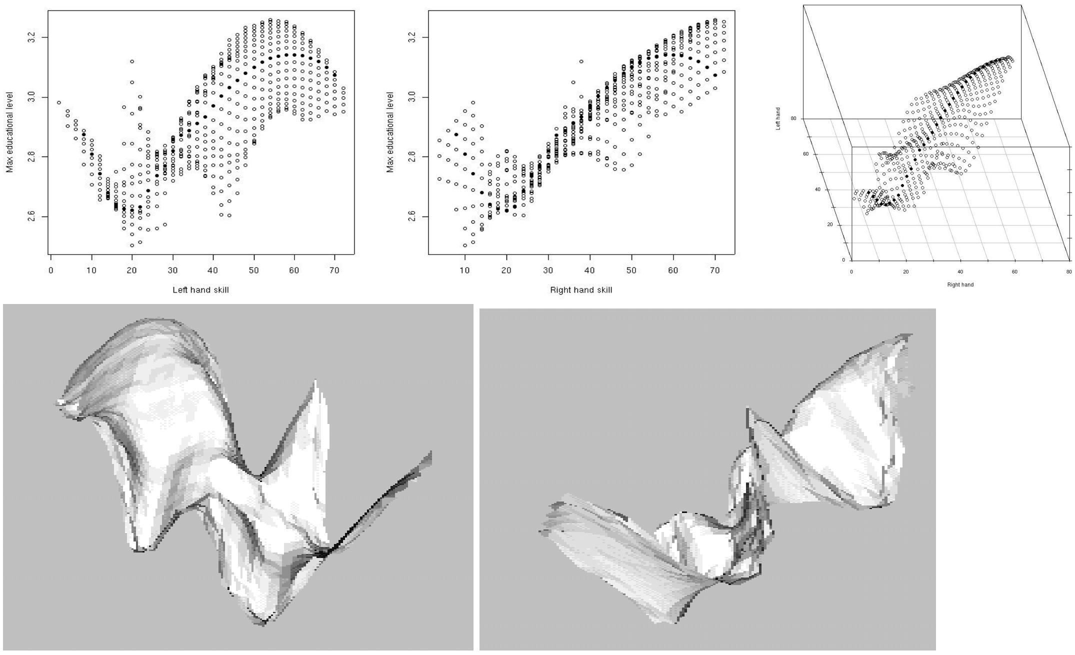


Figure 11a: Max education vs match-picking - NCDS

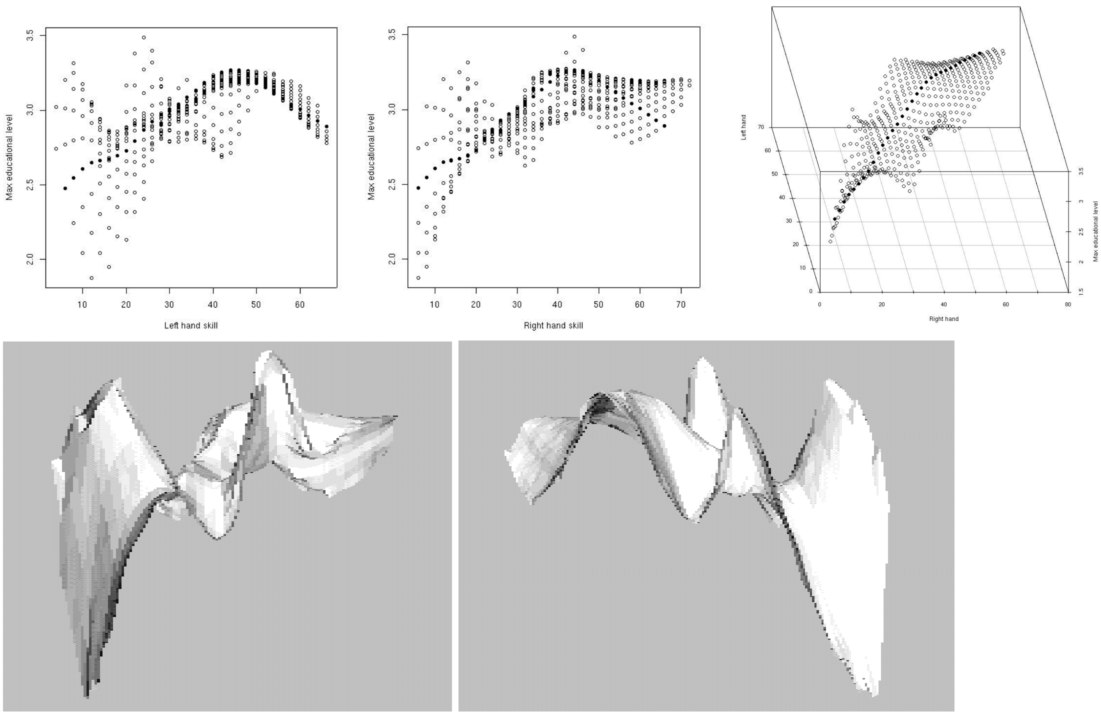


Figure 11b: Max education vs match-picking - BCS70
Total deviation ~ 10% of scale (~0.6(NCDS) 0.8 (BCS70)/6)
This is similar in shape to the cognitive measures - a midline hump, 'ears' either side in the middle, dropping off towards the origin.

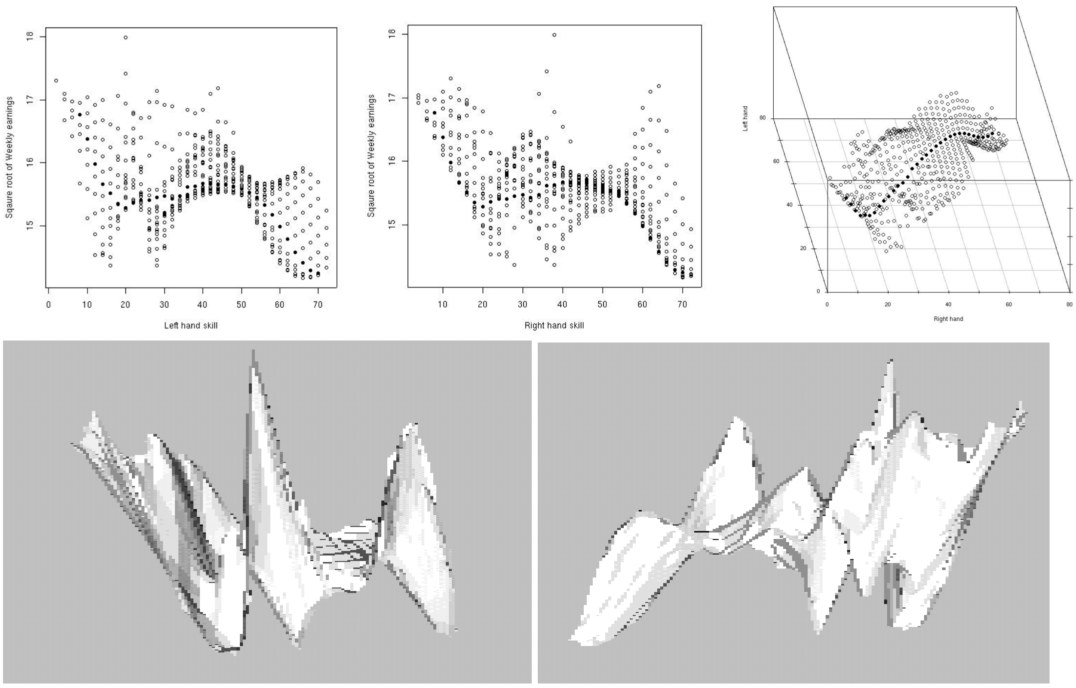


Figure 12a: Square-root of earnings per week vs match-picking - NCDS

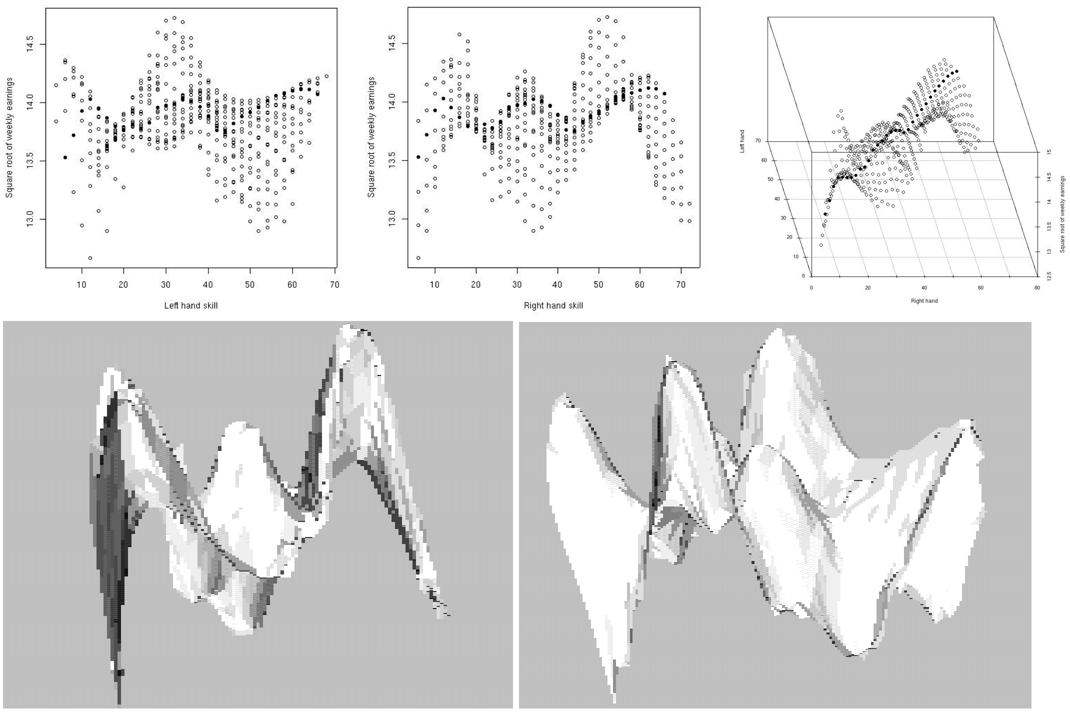


Figure 12b: Square-root of earnings per week vs match-picking - BCS70
Total deviation ~ 3% of scale (1/30). Complex contours, if anything falling off towards high values.

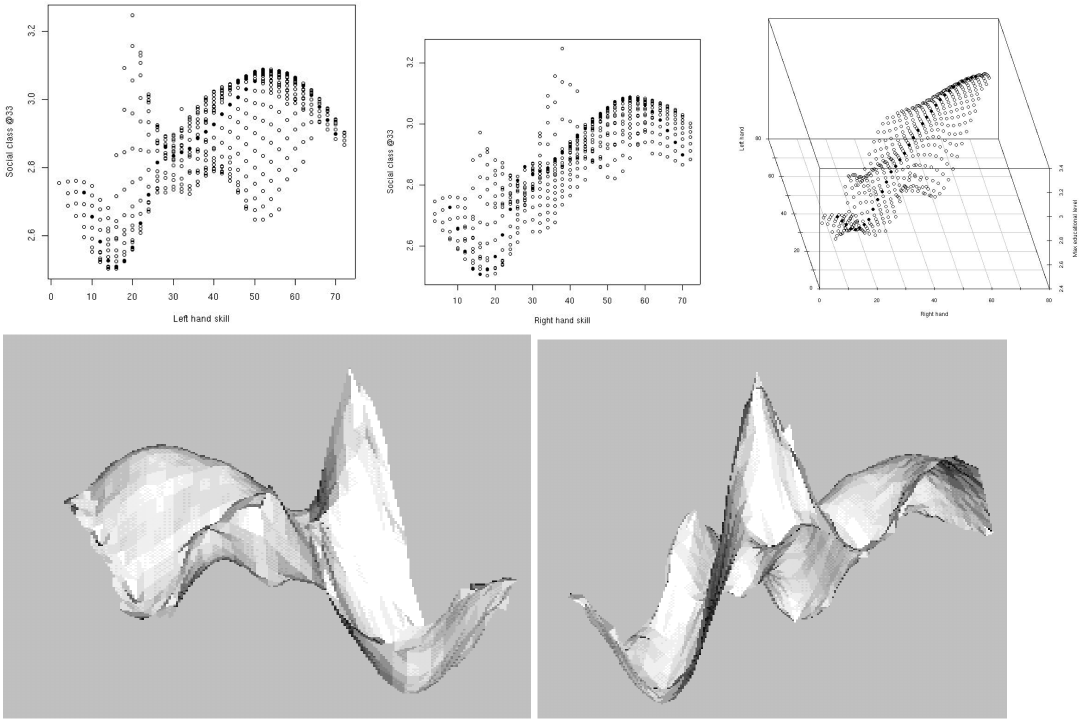


Figure 13a: Social class @33 vs match-picking - NCDS

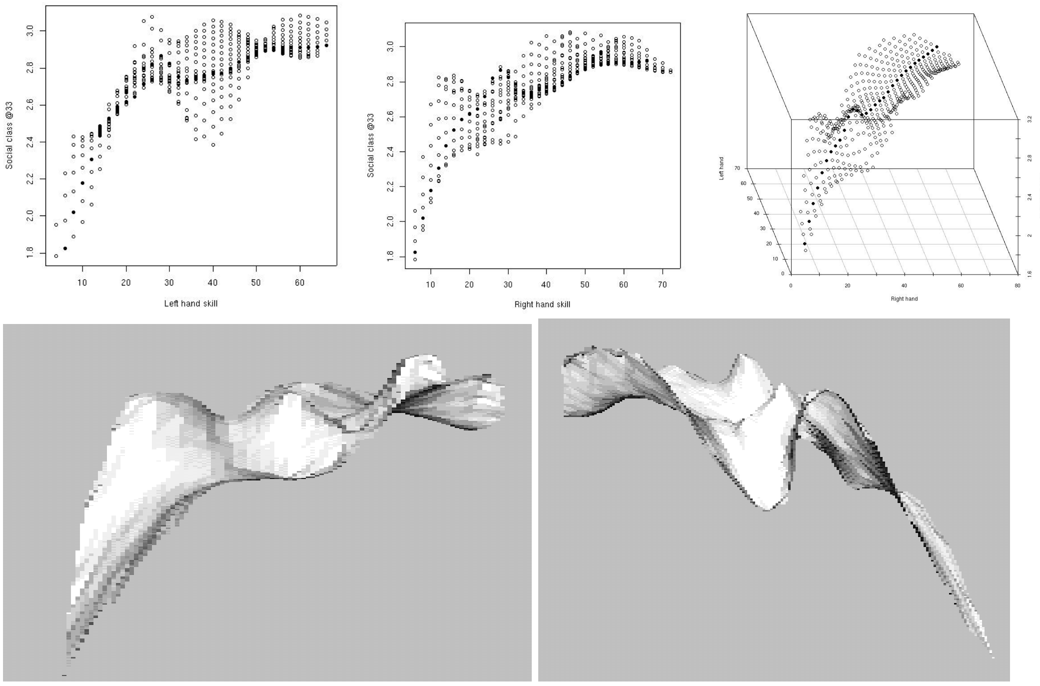


Figure 13b: Social class @33 vs match-picking - BCS70

Total deviation ~ 8% of scale (0.4/5). Levels off at higher values, falls off (but 'noisier') towards origin.

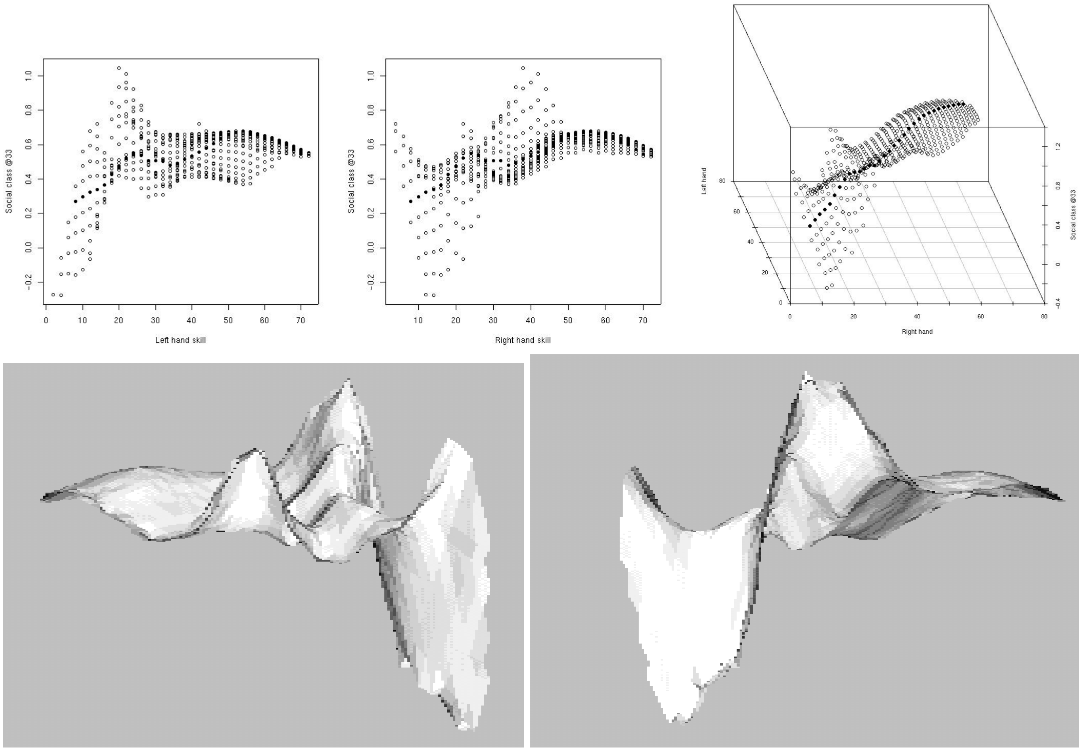


Figure 14a: Social class difference vs match-picking - NCDS

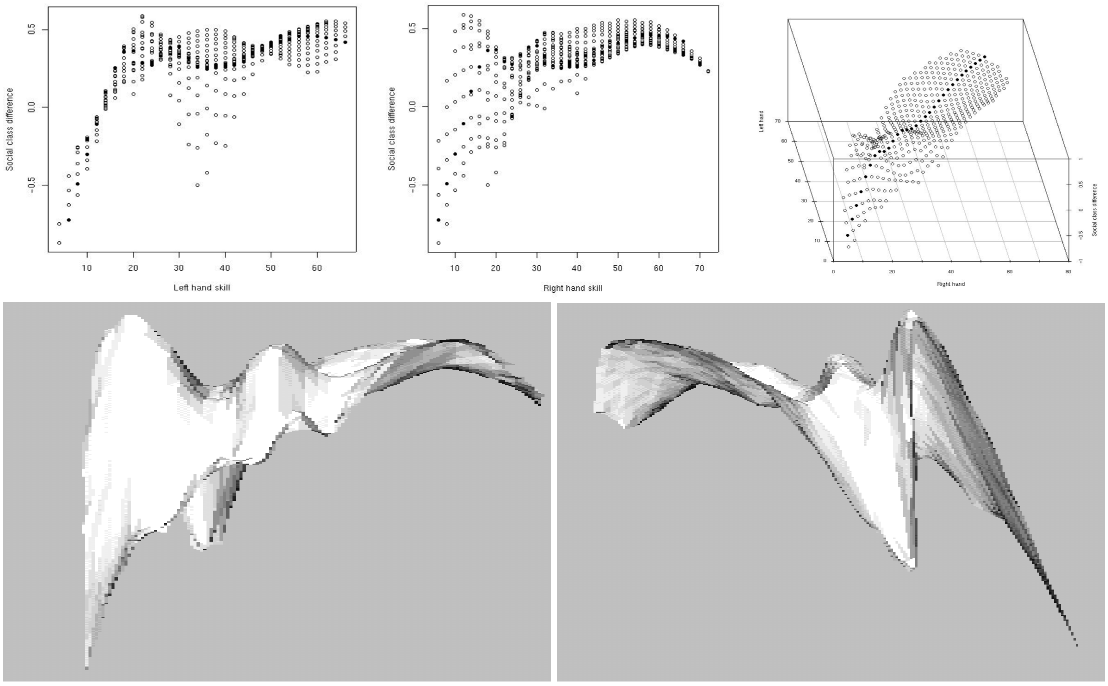


Figure 14b: Social class difference vs match-picking - BCS70
Total class difference ~12% of scale (1/8). Midline fairly flat again, some fall off and again increased noise towards zero.

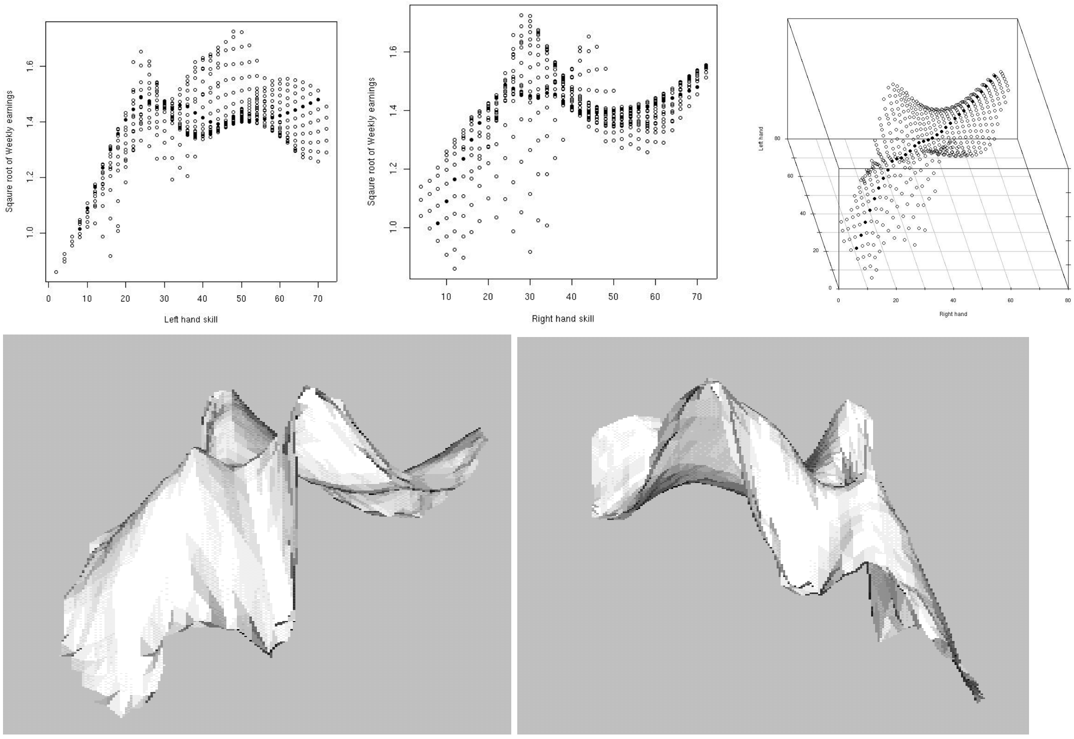


Figure 15a: Number of offspring @33 vs match-picking - NCDS

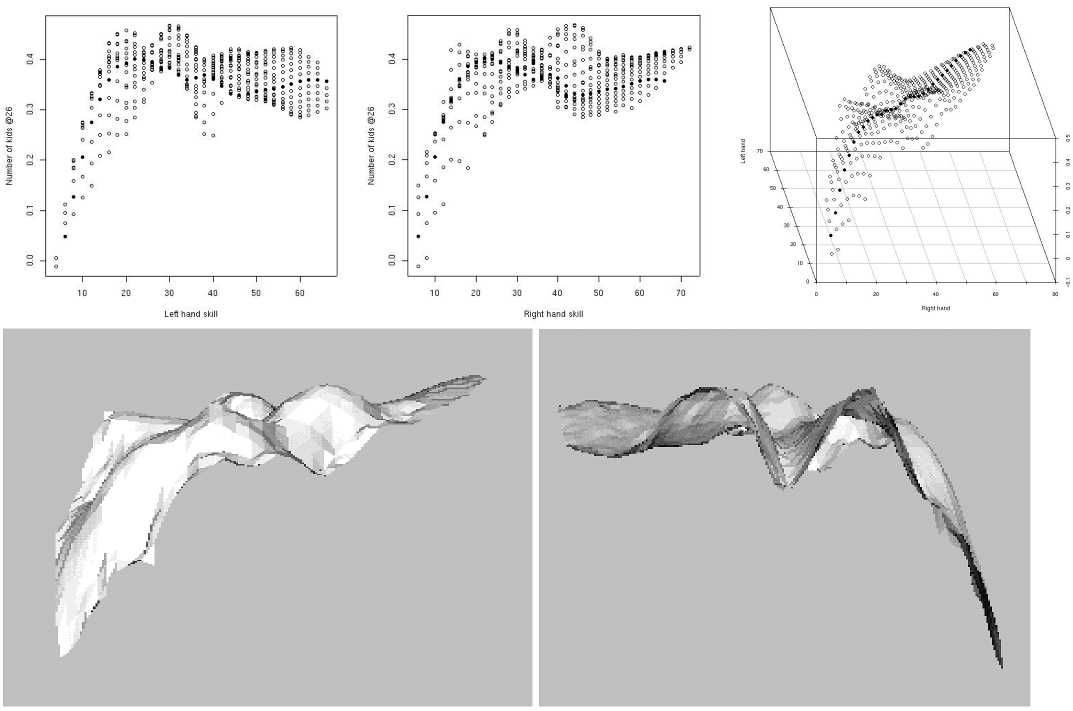


Figure 15b: Number of offspring @33 vs match-picking - BCS70

Total deviation of midline ~ 10% of scale (0.8/8 (NCDS), 0.4/4 BCS70)

Fall off towards origin. Relative dip at midline for average skill.

Discussion

The correlations with box-marking are for the most part greater than for match-picking. Further, the box-marking figures appear less chaotic and more informative than the match-picking figures. Sadly, there are no measures in BCS70 with which to compare the NCDS figures on this measure.

The relationships in box-marking for the most part echo the cognitive measures, with performance falling off towards the midline and the origin, and increasing with increasing hand skill.

The relationships with match-picking are smaller in magnitude. Thus noise, outliers etc. may account for those figures where outcome drops off as you approach extremes of skill. Alternatively, it may also reflect that Machiavellian intelligence is not the same as skill at word recall. There is a sense of consistency between figures from each cohort on a given measure eg. earnings are more 'chaotic' than social class difference.

Psychiatric outcomes versus lateralization

Method

'Psychological function' measures

Given the follow-back data-gathering exercise described in chapter 6, the opportunity arose to add measures of poor psychological function to the general measures above. The data was gathered with a view to examining schizophrenia in particular, with the result that other outcomes present in the data, will be biased in favour of cases with features that make admission to a psychiatric hospital more likely. This latter might include features as basic as the presence of threats of self-harm, or past history of the same. Nonetheless, the decision to admit is based upon some assessment of need for asylum, however acute, which does not suggest an assessment of optimal psychological function.

As a result, it seemed interesting to explore the associations between sidedness measures and the following outcomes:

- admission to a psychiatric hospital as an outcome
(a useful comparison group. Any findings here point to psychological difficulties, but not necessarily mental illness)
- affective disorders
(ie. Those with a major mood disorder)
- schizophrenic illness
(ie. Psychosis without major mood disorder)

The Kraeplinian dichotomy separates disorders of mood, which if severe may include psychotic symptoms such as delusions or hallucinations, from psychotic disorders without a clear mood disorder. This might predict categorical differences between the distribution of these two groups, whereas a continuum view of psychosis may show differences in degree only. Hence schizophrenia is to be compared with affective disorder with or without psychosis.

Statistics

Insufficient cases in BCS70 to pursue match-picking

The number of cases in BCS70 was small. This, coupled with the failure to observe any consistent relationships in verbal surfaces using the match-picking measure, led to a decision not to pursue these figures further.

NCDS box-marking surfaces

Numbers of inpatients were large enough to estimate a verbal skill surface, for comparison with the population.

'Flat' group mean calculated for clusters of cases, rather than locally-weighted mean surfaces.

Numbers of cases of schizophrenia and affective disorder were not large enough to generate meaningful locally-weighted surfaces - local estimation degenerated into single-case values with such a small N, and the variance made comparison with the population mean surfaces impossible. As an alternative, then, group means were calculated for each outcome cluster.

However, the density estimates of schizophrenia did suggest 3 'groups' of cases. Hence cases were divided up into 3 groups using cluster analysis, and mean verbal scores calculated for each, thus capturing some feel for 'local' values.

Of course such a division of schizophrenia cases into 'hand skill zones' is potentially arbitrary, and if anything the plots suggested that, overall, the pre-affective & pre-schizophrenic cases covered much the same areas in 'hand skill space'. Thus cluster analysis was then also used to split the affective disorder cases up into 3 groups. The two figures, one with one big group of affective cases, one with three sub-groups, were compared.

Uncertainty and effect size

Once again, the small numbers of cases of illness meant that differences were for the most part non-significant, although analysis of variance did show the schizophrenics in the NCDS cohort to be significantly verbally-handicapped ($F_{(1,11773)}=9.8$, $p=0.0017$) with respect to the population.

Results

NCDS	N	LH:RH (% LH)	Female:Male
Population	12613	1306:11307 (10.3)	5679:5934
Psychiatric in-pts	163	17:146 (10.4)	80:83
Affective disorder	36	6:30 (17)	19:17
Schizophrenia	28	6:22 (21)	18:10

BCS70	N	LH:RH (% LH)	Female:Male
Population	11784	1357:10427 (11.5)	5736:6048
Psychiatric in-pts	62	5:57 (8.1)	27:34
Affective disorder	10	2:8 (20)	7:3
Schizophrenia	9	0:9 (0)	4:5

Table 3: Psychiatric outcomes versus hand preference & sex

Lefthanders are under-represented in the BCS70 inpatient group, although numbers are smaller overall. Lefthanders are over-represented in all patient groups apart from in the (small number of) BCS70 pre-schizophrenics.

NCDS - box-marking index	Males RH	Males LH	Females RH	Females LH
Population	15.9 (9.1)	-13.9 (10)	16.5 (9)	-13.9 (11)
Psychiatric in-pts	16.5(10)	-12.9 (8)	14.7 (12)	-14.7 (9)
Affective disorder	18.0(7.5)	-14.9 (8)	12.6 (13)	-5.7 (11)
Schizophrenia	7.1 (14) n=7	-16.2 (7) n=3	15.2 (12) n=1	-20 (2) n=3
NCDS - match picking index				
Population	0.7 (9)	-3.8 (9)	1.3 (9)	-3.2 (9)
Psychiatric in-pts	2.2 (8)	-1.6 (15)	1.8 (9)	-6.0 (14)
Affective disorder	3.2 (6)	-0.7 (21)	2.7 (9)	-15.3 (14)
Schizophrenia	2.6 (9)	-4.7 (11)	0.6 (8)	3.8 (8)
BCS70 - match-picking index				
Population	0.81 (9)	-3.5 (9)	1.4 (9)	-3.2 (9)
Psychiatric in-pts	-.97 (8)	-12.7 (8)	0.6 (8)	4.0 (9)
Affective disorder	10.2 (6)	NA	-1.9 (6)	3.8 (13)
Schizophrenia	-3.6 (7)	NA	-3.5 (9)	NA

Table 4: Psychiatric outcomes versus laterality indices (sd)

Box-marking: Inpatients show a loss of the female right-superiority. Female affective and male schizophrenics also show large drops in lateralization index. Numbers of cases are too small to allow these differences to achieve significance in these sub-groups.

Match-picking: These results are unimpressive - the small numbers of cases combined with the small deviations from zero anyway make the results uninterpretable.

Scatterplots of hand performance by group (figure 16):
Box-marking: The in-patient population distribution looks very similar to the normal population, as does the affective disorders group. The schizophrenics on the other hand appear to form at least two groups (one each side of the line of equal hand skill), if not three (with a 'low-performers' group nearer the origin).
Match-picking: Inpatients resemble the population, cases cluster around the line of equal hand skill ie. if there are differences, this approach cannot resolve them.

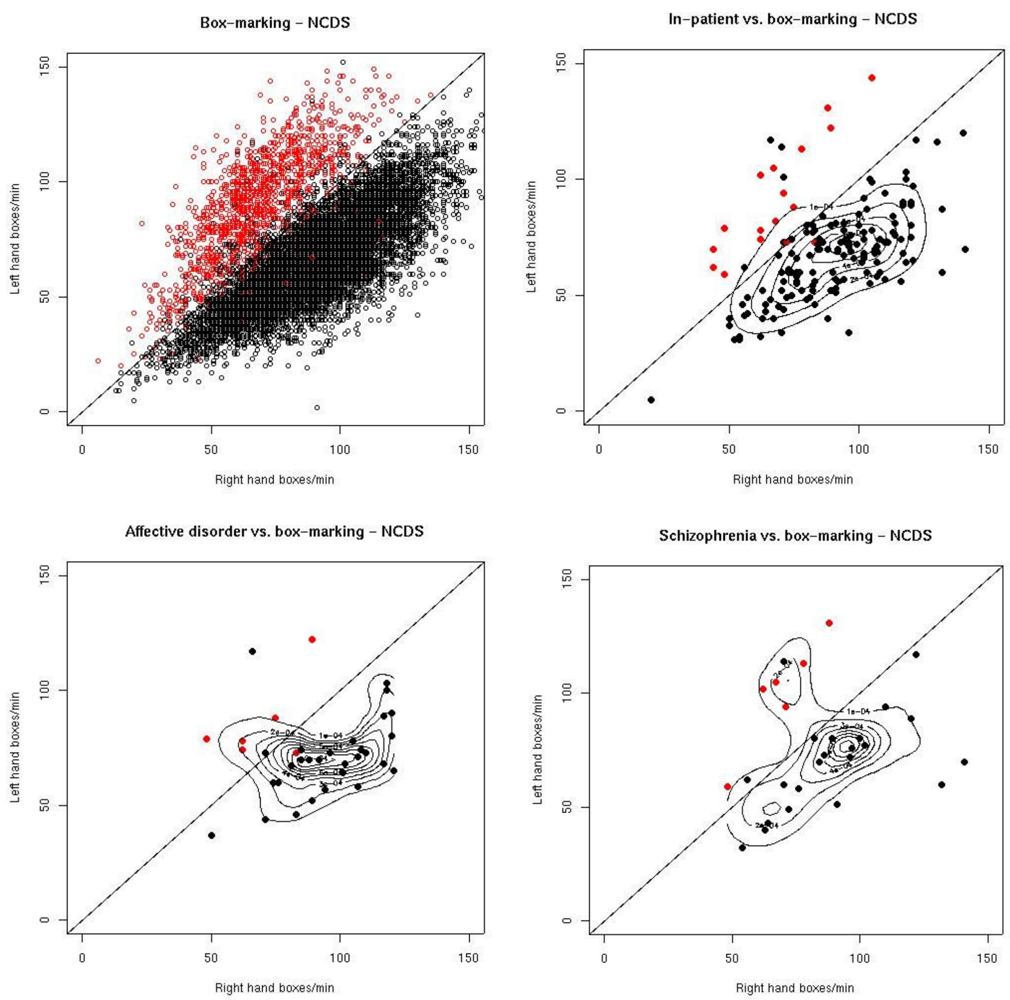


Figure 16: Population, Inpatients, Affective Disorder and Schizophrenia cases vs box-marking (NCDS)
(Black = Righthanders, Red = Lefthanders)

Verbal skill by group (table 5):
In-patients were down compared to the population. Affective disorders were better-performing on average, and the premorbid schizophrenics were the worst of the lot. The cases were grouped as discussed in the statistics section above, and plotted on the verbal surfaces. This was only carried out for box-marking, given the low correlations and dispersion with match-picking.

Population:	22.4
In-patients:	18.5
Affective disorder:	20.0
Schizophrenia:	16.9
- cluster 1	12.3
- cluster 2	17.6
- cluster 3	22.3

Table 5: Mean verbal score by diagnosis

Inpatient verbal surface (figure 19):
Similar to the population one in shape. However, from the Z-axis on this, and direct comparison with the population figure (figure 20), it can be seen that on the whole verbal skill differences are greater for this group, with verbal skill exceeding that of the population only at middling ranges of righthand and lefthand superiority.

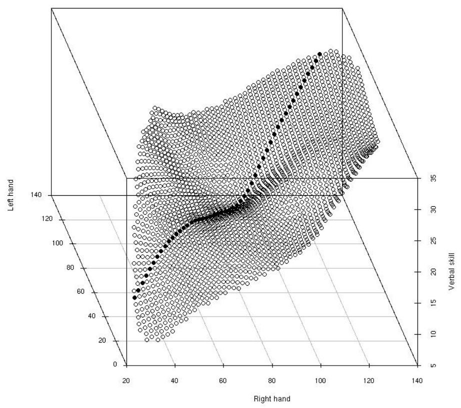


Figure 19: In-patients: Verbal score vs. box-marking - NCDS

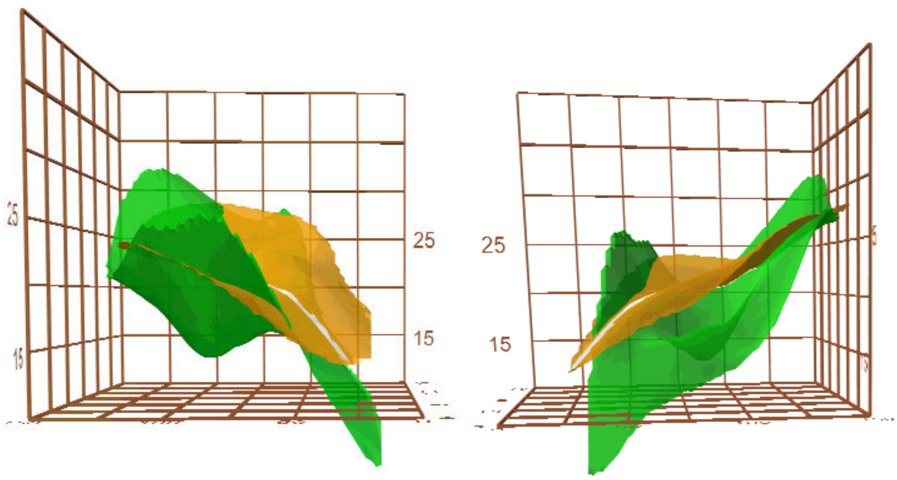


Figure 20: In-pt (green) verbal vs population (yellow) - box-marking - NCDS

Affective disorder and schizophrenia verbal skill (figures 21 & 22):
It can be seen that the bulk of the schizophrenic group are more verbally-impaired than the affective disorder group. The two sub-groups consist of lefthanders, with subnormal (but better than affective disorder) verbal skill, and another group whose verbal skill is far worse than their hand skill would predict. Dividing affective disorders into 3 groups in a similar manner to the schizophrenic group has little effect apart from showing a more verbally-handicapped lefthander group (in contrast to the top-performing schizophrenic lefthander group).

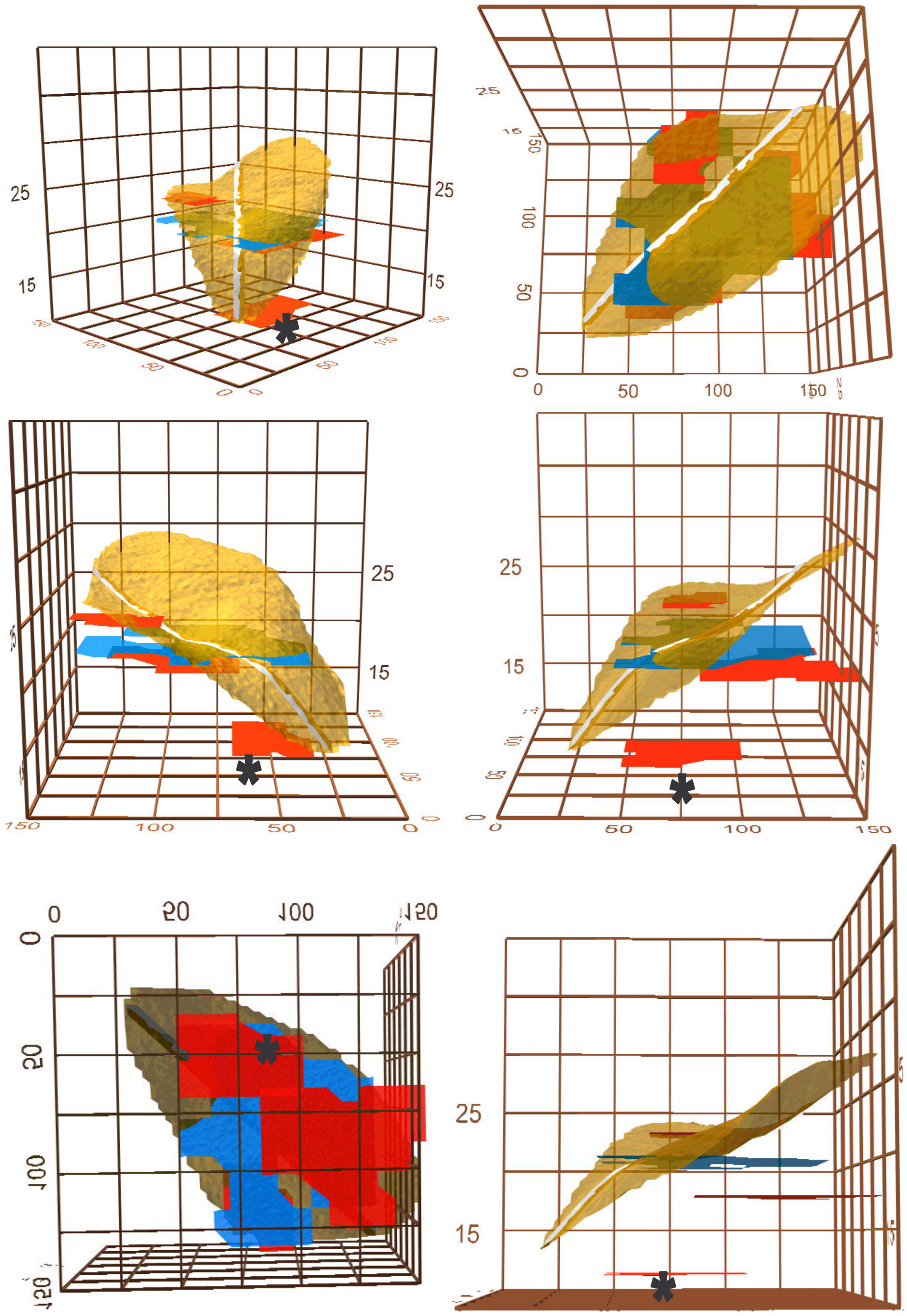


Figure 21: Verbal skill vs box-marking - NCDS
- Schizophrenia (red) 3 groups, Affective disorder (blue) as a single group
- Note low-performing schizophrenia group (✱)

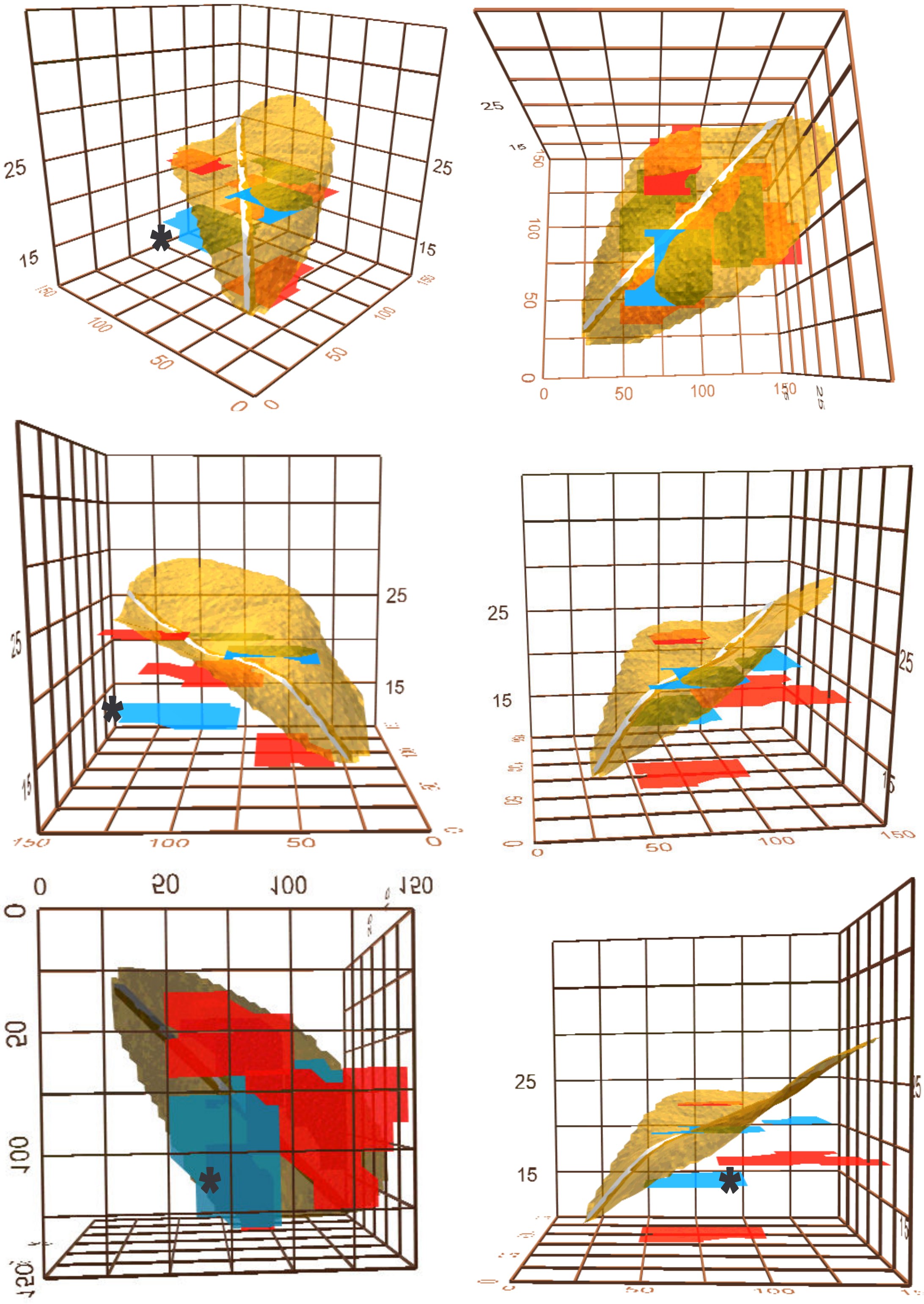


Figure 22: Verbal skill vs. box-marking- NCDS
- Schizophrenia (red) 3 groups, Affective disorder (blue) 3 groups
- Note the low-performing lefthanded affective disorder group (blue) (✱)

Discussion

The relationships between the groups' verbal skills apply regardless of the laterality measures used to distribute them on the x-y plane. However, it is only the box-marking measure that seems to distribute them differently by outcome group. This may simply be a problem of resolution, as noted previously for the match-picking task (McManus 1985).

Verbally, the inpatient population as a whole performs poorly, which would be consistent with a view that this population are poorer-equipped generally to cope with the difficulties life brings. The affective disorder cases are less handicapped on average, suggesting more that it is specific mood disorder that has put them into hospital.

Schizophrenia is associated with a greater verbal deficit than affective disorder, as well as a decrease in overall lateralization. However, this is a characteristic of the group, not individuals - the variance is large.

Whether the sub-groupings by 'laterality space' have any validity is unclear, although it is reassuring that sub-grouping affectives does not merely echo the findings in schizophrenics. Overall, it is more satisfying to have found a measure that can distinguish the schizophrenic group from the affective group qualitatively (the shape of the density distribution) as well as quantitatively (the laterality and verbal measures).

The warning has to be that the numbers of cases are small. Although the density estimate figures for each diagnostic group appear quite different (fig 16), the mean verbal skill 'plaques' (not weighted for local density) for each group largely overlie each other (fig 21). The variance in test scores is very large compared to the displacement along the z-axis of each of the case groups from the population. That the means lie where they do, given as few as three cases per group, is perhaps fortunate in the extreme! It is not entirely obvious how the picture would change if the numbers of cases were increased.

Conclusions

Box-marking skill appears to distribute the population and cases well, accounting for variance in verbal skill that is fairly easy to appreciate - the 'valley' up the line of equal hand skill. This relationship is reflected to a greater or lesser degree in all the adult outcomes studied. Good performance at cognitive tasks and in life are associated with box-marking hand skill asymmetry away from the midline for most people.

For match-picking the picture is less clear - apart from a fall-off near the origin, and a small increase in values near the line of equal hand skill, the relationship is far less convincing.

Psychiatric illness is associated with poorer verbal skill, except at extremes of right and left-superiority. The previously-documented loss of asymmetry in premorbid schizophrenia seems to be due to an over-representation of lefthanders, with superior left hand performance. Verbal skill is worse than the population in the bulk of premorbid schizophrenics; this poor outcome is not just due to an identifiable subgroup of very handicapped individuals.

Thus it is possible to interpret findings related to asymmetry without recourse to laterality indices, and their associated complexity and confounding. Relationships are clearly-identified with respect to left-right differences, and overall performance.

Chapter summary

Representing adult outcomes in relation to bivariate hand skill measures proves informative and interpretable. The relationships between adult outcomes and hand skill asymmetry appear robust with the box-marking measure.

Small groups of interest can be plotted on these figures and compared with the population and each other, placing any differences in the context of asymmetry and overall performance.

Thus, laterality indices can be avoided, to give three-dimensional figures that appear richly informative about the nature of these relationships.

Chapter 10: General discussion

Introduction

The numerous analyses presented in this thesis represent an exploration of the relationship between the continuous measures of functional lateralization and measures of psychological performance present in the cohort datasets. The findings can be summed up as attempts to answer the following questions, essentially the questions posed at the end of the Introduction (page 8):
1. What is the distribution of higher cognitive function with respect to lateralization of hand skill?
2. What is the distribution of hand skill with respect to lateralization of hand skill?
3. What is the mean distribution of hand skill?
4. Does analysis in 3D help clarify any of the above issues?
5. Do the findings generalise beyond abstract measures, to real advantages that might impact upon natural selection?
6. Do the findings shed any light upon the reported loss of brain asymmetry in schizophrenia?

Each of the first three analyses, although exploratory in nature, resulted in findings that can be clarified in terms of a more specific question:

1. Is there a relationship between brain function and lateralization of that function? If so, where is function poorest?
2. Is brain function maximal at some consistent degree of lateralization?
3. Is there evidence that lateralization itself is being maximised or limited?

(it should be borne in mind that these are not a priori hypotheses, and therefore there are no post-hoc test statistics presented here).

A discussion follows of each of these points, followed by a discussion of their implications for three important theories, the Annett Right-Shift Theory, the McManus Model of Handedness, and the Crow Hypothesis. However, before proceeding further, it seems useful to clarify the issue of the effects of practice, as these have been raised several times as an important difference between the two laterality measures analysed.

Function = Practice = Lateralization?

A task such as box-marking can be argued to be closely allied to skills used in writing. It can therefore be argued to have been unimanually practised for many years in all subjects that have been tested in the literature discussed earlier. Conversely the symmetrical distribution of match-picking skill suggests that either the task is un-practised, bimanually practised, or that whatever practice has taken place has produced little response so far.

If box-marking <u>is</u> more unimanually-practised than match-picking, this observation alone may account for a relationship between laterality and level of function. A reasonable definition of an individual being more intelligent than another is that their performance will respond better to practice. A more intelligent individual's performance at a task will improve more or faster after a given amount of practice than that of a less intelligent individual. Even if 'ability to benefit from practice' is not the same as intelligence, that the two should be correlated is surely to be expected. This being the case, if unimanual practice by the preferred hand takes place, function in that hand will improve relative to the other hand: the functional lateralization of performance on that measure will increase.

Magnitude of laterality in a practised task may therefore inevitably show an association with cognitive function. Indeed, such a relationship could be seen as a matter of definition. However, this is not the same as saying that this relationship, between cognitive function and functional lateralization, is merely an artefact. Many brain functions develop <u>as a consequence</u> of repeated stimulation in specific brain areas.

It is the repeated stimulation of occipital cortex by signals from the eye that leads to complex and highly-specialised differentiation required for mature visual cortex function. Without the stimulation, the functions do not develop in the first place.

[Support for this position can be seen in experimental literature observing that input to a developing brain area influences its development in important, measurable ways (eg. White, Coppola & Fitzpatric 2001). Functional capacity is not simply derived from the genetic blueprint. Another important literature is that on recovery of function after brain injury, with the apparent taking-up of functions from damaged areas by other brain areas (eg. Hertz-Pannier et al. 2002). This demonstrates plasticity of functional anatomy in response to changes in need for that function. Computerised "neural networks" also work after this fashion, in that they are initially 'trained' to function in certain ways by being fed 'training sets' of example data which modify the strength of connections between nodes in the network. The relative effects of nature & nurture in the human brain is a huge area which I will not go into further, beyond observing that nurture has important effects on functional anatomy.]

Thus, in the brain there is a sense in which lateralization (or at least localisation) of function *and the function itself* arise due to 'practice'. Variability in cognitive function may be reflected by variability in brain localisation. And the localisation can be measured, as lateralization. From a developmental perspective, the lateralization is the fundamental variable, and the level of cognitive function is a consequence of this.

It may be noted that two predictions will follow from this model:
1. Lateralization will be correlated with any measure of cognitive function that shares function in common with the tasks used to derive the lateralization in the first place. If this is the only process that is taking place, this is the only relationship predicted. In a population sample, the variation seen in cognitive function will reflect the variation in lateralization of the function.
2. Sign of lateralization will be distributed according to hand preference, as this dictates which hand is doing the practice. There will of course be a normal spread of

final values as a consequence of environmental influences on both this and other aspects of neurodevelopment.

1. What is the distribution of higher cognitive function with respect to lateralization of hand skill? (Is there a relationship between brain function and lateralization of that function? If so, where is function poorest?)

The findings from the NCDS cohort box-marking task seem unequivocal - there is a relationship between lateralization of box-marking and a variety of measures of cognitive function. More specifically, cognitive function is poorer near symmetry of hand function.

Laterality as measured using the match-picking task did not show this relationship; plots against IQ were fairly flat.

The box-marking result compares favourably with Annett & Manning's 1989 original report using the peg-board task. However, it is noted that the original effects size was over-estimated (Annett 1993), and some attempts to replicate this finding have failed (eg. Mayringer & Wimmer 2002). Analyses using box-marking or match-picking alone in other datasets could not be found.

Laterality derived from Peg-boarding, as with box-marking, is asymmetrically-distributed in the population, although it appears as a single distribution. One might interpret this as the task being partially-practised, at least by the age of testing. However, the status of peg-boarding as initially measured remains a conundrum. Is it entirely unpractised, and the distribution shifted from the midline by some primary process? Or is it a mixture of two or more partially-separated distributions that still overlap a great deal?

The asymmetry in peg-boarding laterality might be a 'linked asymmetry' ie. some aspect of the function is already lateralized by being involved with some other process lateralized in some other way, and the former is only 'partial', not yet maximised by explicit practice. The effect unimanual practice at this task would have on the distribution is perhaps possible to anticipate: two distributions might separate, as a function of the preferred hand that was practising, leading to a distribution similar to that seen for box-marking.

An alternative view might be that if one practised box-ticking with both hands, the distribution might coalesce into a single distribution. Would this result in an asymmetrical (like peg-boarding) or symmetrical (like match-picking) distribution? Scope for some experimentation, perhaps; although there is data suggesting that bimanual practice has little effect on peg-boarding laterality quotients (Tan 1990), such data is not available for box-marking. However, the fact that the population means for right and left-hander groups are very similar suggest the result would indeed be a distribution symmetrical around zero. That peak left-hand performance in lefthanders is less than peak right-hand performance in right-handers suggest it would be displaced from zero, in a positive direction, but by some finite amount.

It has been reported by McManus et al (1992) that in several handicapping conditions, preference remains intact but performance differences are lost. In a dataset where all handicapped individuals are not identified, and therefore cannot be removed and the analysis repeated, we are left with this as an alternative account of a drop in cognitive function near symmetry; individuals with a whole variety of intellectual handicap will be over-represented here.

Overall, then, the finding is that there is a drop in cognitive function around symmetry. We have one side of our triangle of associations, although it may be mediated via pathological processes alone.

2. What is the distribution of hand skill with respect to lateralization of hand skill? (Is brain function maximal at some consistent degree of lateralization?)

The 'lagging' analyses (page 108-7) allows correct interpretation of these otherwise highly-confounded plots.

Previous findings related quantitative skill or dimensional measures to laterality indices derived from them (Annett & Manning 1989, Galaburda et al 1987, Tan 1990). These were (mis)interpreted as showing that "degree of laterality is achieved not by differing levels of superior-side performance, but differing levels of inferior-side deficit". However, a measure of performance that contains a great deal of noise, when plotted against a given function of that performance and smoothed will merely show the distribution of that given function. Leask & Crow (1997 - see page 97) use an approach that takes this into account, re-stating the research question in terms of an alternative 'null hypothesis'.

The finding from this analysis was that hand skill is maximised at a degree of about 10% displacement of lateralization from the midline. The finding that performance is maximised in the population at a certain degree of left-right difference is then supported by the later improved analysis that enlarges the setting and demonstrates the uncertainty in this finding (see page 108). The second analysis confirms that ~10% relative laterality is associated with some degree of maximal hand performance, 10% right superiority in right-handers and 10% left-superiority in left-handers.

Hand skill is maximised at ~10% lateralization in both hands, in both measures, in both cohorts. This is a remarkable finding, given that in most respects the two measures of hand skill are very different. Although at best a trend in the match-picking measure, nonetheless there is a compelling degree of similarity in the position of this maximum in the two measures and two cohorts.

It stands in contrast to the resounding negative findings relating left or right-handedness to cognitive function (see page 45). However, it might support the findings suggesting that 'mixed handedness' is associated with some deficit as individuals with mixed preferences demonstrate lower performance differences.

If the population histograms for these measures are examined (see Table 4, Chapter 8 - page 105) it can be seen that these 10% laterality points do not coincide with that degree of lateralization is further out (~16%) for box-marking, and further in (~1%) for match-picking. Thus degree of lateralization of hand skill may have been under selective pressure in the past, but is no longer. That hand skill laterality is commonest even further away from symmetry than maximised hand skill suggests that this may again be a linked asymmetry, linked to some function that is even more lateralized in the population eg. language.

Once more the critique might be that hand performance is being skewed, by over-representation around zero lateralization of handicapped individuals. As before, this analysis cannot resolve this question. (It is also possible that the finding of a peak near 10% laterality is an artefact of this new analysis method, given the remaining methodological undesirability of plotting dependant variables – it still doesn't quite feel right.)

The triangle of associations again has at least one side, from this different perspective.

3. What is the mean distribution of hand skill? (Is there evidence that lateralization itself is being maximised or limited?)

It has been suggested above that cognitive performance is a function of the degree to which the function is lateralized, and some evidence presented above to suggest that there is an optimum degree of lateralization for hand skill (at least).

If functional lateralization is a fundamental quality of individuals, how does it vary in the population? Is there evidence that the development of lateralization is constrained in any way?

Absolute lateralization of hand skill shows an inflexion near the middle of the population; it increases up to a point, then either levels off or decreases depending on how laterality is conceived, as hand skill increases (see page 127). As has been discussed, this approach to examining the distribution of a lateralization measure appears novel, and the straight lines that have emerged from a non-parametric approach are intriguing. The two gradients are especially interesting; each on its own seems explicable; the early slope relates general ability to the effect of unimanual practice. The parallel line suggests some ceiling on whatever is leading to the earlier slope.

It is unclear why the inflexion occurs where it does, or what the origin of this ceiling might be. The earlier slope away from symmetry might reflect a concentration of handicapped individuals near symmetry, but with poor performance, skewing the line away from its otherwise 'fixed' degree of laterality. Again, it is not possible to comment further, except to say that the plots really do look as if there are just two different straight mean distributions.

The ceiling may be genetically-determined. This would be compatible with theories predicting fixed degrees of lateralization (eg. see later discussion of McManus theory).

The similar plots for the 'un-practised' match-picking measure shows lines perhaps too close to x=y to interpret beyond saying that for this task there seems to be little in the way of lateralization in the population overall, which is clear from previous plots.

Deviations at high values of hand performance are in areas sparse on data points, and thus of questionable significance.

This again suggests, from yet another perspective, some substance to that side of the triangle of associations; there is something beyond chance associating degree of brain function and lateralization of that function.

4. Does analysis in 3D help clarify any of the above issues?

The 3D plots are undeniably elegant, but their utility must be questioned given the technical difficulties associated with them. They are complex to generate, require large numbers of data points, and are best visualised on the computer screen as three-dimensional models, as even the most careful rendering leaves them difficult to interpret as 3D projections onto the 2D page.

However, for the box-marking measure the relationship between asymmetry and cognitive function seems very clear (figure 20, page 134). Cognitive function increases with hand skill generally. It levels off in the middle section, while decreasing towards low and increasing towards high levels of hand skill. It increases too as you move away from the line of hand skill symmetry. Lower-performers are handicapped at extremes of right-hand superiority.

This figure addresses at least one issue left unresolved by the previous (two-dimensional) figures. We can see that symmetrical hand performance is related to lower IQ throughout the figure. Not just at the lower-performing end where one might anticipate finding a concentration of handicapped individuals.

One might attempt to retain the notion that IQ and laterality are unconnected by generalising the 'handicapped groups' argument into the general population: disordered neurodevelopment may be expected to interfere with development of higher cognitive functions and functional asymmetries across the population. At whatever level an individual might perform, if their neurodevelopment is interfered with by random environmental insults they will end up lower-performing, and more symmetrical. However this re-definition of the term 'handicapped' perhaps just confirms the finding, rather than confounding it.

Match-picking is less satisfactory as a measure, relationships generally being flatter and not segregated by writing hand (see figure 29, page 140). However, the figures do provide some validation for the technique given the effects seen for the box-marking measure. There is a dip in IQ for the very poor hand performances, demonstrating that the IQ measure used is picking up individuals with very poor hand skill. These sudden 'crashes' in IQ are in contrast to the smooth gradients seen in box-marking figures, and perhaps are identifying individuals that might be considered functioning at a pathologically low level.

There seems a fairly consistent 'midline ridge', showing best IQ along the line of symmetry – any asymmetry on this measure relates perhaps to random influences, being in the tail of a distribution, development not where it 'should' be. The effect is small and inconsistent between cohorts ie. ridge unclear in BCS70 figures (figs 33-35 chapter 8, page 142).

Overall the 3D match-picking figures demonstrate the relationships between IQ and hand skill that one might expect. Very poor hand performers are also not too smart - the measures are valid - but a consistent, convincing relationship between IQ and lateralization of hand skill is absent. The explanation could be just that the task is as yet un-practised.

So our three-dimensional figure not only demonstrates again the 'function - laterality' side of the triangle, but clarifies some of the ambiguity about this relationship that characterised the two-dimensional figures.

5. Do the findings generalise beyond abstract measures, to real advantages that might impact upon natural selection?

Some genetic models (eg. Annett) call upon an interaction between genes, lateralization, cognitive function, and survival to explain the distribution of laterality and handedness we see today. Cohort data affords a unique opportunity to confirm that any findings don't just apply to abstract measures such as receptive vocabulary, but also correlates with real-world success.

For box-marking, although the figures for different outcomes differ, the main feature of a midline valley with the sides extending outwards hold true whether one is talking of IQ, income, social class or fecundity. For box-marking, although the figures vary between outcomes, they are flatter overall - this looks more like noise.

Clearly the potential for confounding is huge, and that all these 'success' measures and the measures of cognitive function are highly correlated is not surprising. Nevertheless, the demonstration of the relationship in the real world is impressive. While stepwise regression might demonstrate which variables are responsible for most of the variance in this relationship, the issue of validity, when considering genuine characteristics under selection remains.

Alternatively one could argue that these 'success' figures examine outcomes that are just as abstract as the earlier tests, such as position along a certain gradient defined by the societal norms of a single species. However the cognitive and social skills required to attain a relatively high position in human society may not have changed for tens of thousands of years. The intriguing feature of these figures may therefore be that they give us a glimpse, not simply of a correlate of IQ, but the variability underlying it.

Nevertheless, using the three-dimensional representation we can see that the "function-lateralization" side of the triangle of associations impacts upon an individual's performance in the real world.

6. Do the findings shed any light upon the reported loss of brain asymmetry in schizophrenia?

Psychiatric illness seems associated with poorer cognitive function, although this is less of a problem in affective illness. Psychotic illness adds a loss of asymmetry to the findings.

The loss of asymmetry and cognitive function is well-documented (reviewed page 54). Although the numbers of cases in this analysis are low, these measures are at age eleven, long before the illness manifests itself, so any differences seen are differences in neurodevelopment. They are not a result of attribution bias, a direct manifestation of psychotic symptoms, or an effect of medication.

Schizophrenia is seen as a condition of disordered neurodevelopment. We must be clear that this figure suggests there is a difference in how asymmetry is distributed in the population of cases. It does not suggest there is a difference in any individual's asymmetry; the case groups do not appear closer to the line of symmetry compared to the population. The overall mean laterality for the cases appears more a consequence of the excess of left-superior individuals, rather than the group of poor-performers with their correspondingly low laterality.

Thus we could conclude that further study of this symmetry measure in schizophrenia is fruitless; it is not the individual's asymmetry that is characteristic of the illness, but the distribution. The interesting feature here, surely, is whatever it is that is determining how asymmetry is distributed in this group. Similarly, studies of the distribution of binary preference may prove of little use, because the asymmetry is not disordered; it is just distributed differently. Remembering the principal curve figures (page 127), one might anticipate that the figures for schizophrenics would simply be as for match-picking, not box-marking, although there are insufficient cases to explore that in this dataset. And, finally, asymmetry is distributed differently in a lot of handicapping conditions; whether schizophrenia is substantially different from them in these ways is unclear. The loss of asymmetry seen here may merely flag schizophrenia up as yet another example in which the disordered neurodevelopment is evidenced by a loss of asymmetry; whether the different distribution is related to any specific aspect of the illness is not obvious.

We can see from the three-dimensional figure that the distribution of lateralization in the pre-schizophrenic individuals differs from the pre-affective psychosis individuals, although the degree of lateralization seems pretty similar. We can also see that the pre-schizophrenic individuals are cognitively impaired in relation to both the normal population, and the pre-affective psychosis individuals.

The great strength of this approach is that one can immediately see where cases of schizophrenia lie with respect to lateralization and level of function are with respect to the population.

The difference in cognitive function seems to be of degree, supporting a view of schizophrenia as existing at one end of a continuum. The difference in distribution of laterality appears qualitatively distinct. These similarities and differences would need to be predicted by models of their development.

The great weakness in this part of the analysis is the small numbers of cases in each group. The finding needs replicating in larger numbers of cases before too much emphasis is placed upon there being three ‘Leask subtypes’ (right-lateralized mildly impaired, left-lateralized mildly impaired, and right-lateralized severely impaired) of schizophrenia.

Nonetheless, we can now see not only the “function-lateralization” side of the triangle, but also the “schizophrenia-lateralization” and “schizophrenia-function” sides. The relationships are clearly and unambiguously presented, in the context of the whole-population data. The deficits in function are seen in their lateralized context. It is made clear how they differ from the normal population on exactly what sort of measure. This does seem to be represent beyond numerous woolly statements about ‘less lateralization’, which (as we have seen) can mean almost anything. Where the cases and controls lie with respect to these two constructs, as originally measured, is now clear.

The findings in the context of current laterality research

The findings will now be examined with respect to three theories regarding laterality of brain function.

THE ANNETT “RIGHT-SHIFT” THEORY

Marian Annett’s Right Shift theory makes a key prediction about the relationship between cognitive function and measures of functional lateralization, stemming from the notion of ‘heterozygote advantage’, which suggests that homozygotes for the factor will be cognitively disadvantaged. Unfortunately, given the phenotypic overlap of the three genotypes, negative findings can be easily dismissed as type 2 errors. Nonetheless, the prediction is that anyone demonstrating extremes of left-superiority or right-superiority are more likely to be homozygotes (either two copies of the right-shift factor, or no copies), and therefore to be at a cognitive disadvantage.

The findings above can be seen as equivocal. A chief difficulty is that the Annett model is based in the distribution of the peg-board task, and although predictions should generalise, the findings above are not derived from that measure. It remains unclear what the connection (if any) between peg-moving and box-marking are, especially given factor analyses showing their loading on different factors.

Nevertheless, we can run down the list above and ask which findings support the Right Shift theory. Problems in cognition around symmetry can be seen as supporting heterozygote advantage. The drop-off in cognitive function at extremes of standardised laterality are questionably consistent between the measures (figures 11a,b&c, chapter 8 -see page 121). The 3D figure locates a drop-off in cognitive function only for extremes of right-superiority in low-performers (see figure 20 chapter 8, page 134).

However, although the Right Shift theory specifically proposes that development (specifically of speech) is impaired in the right hemisphere, it is hazy on how other functions will be impaired. Thus even localised disadvantage such as is seen in the 3D figure might be seen as evidence for heterozygote advantage.

Overall it seems that from the 3D figure, examining absolute laterality, the benefit for cognition of increased right-superiority is sustained up to extremes, in support of the connections between practice, function and laterality discussed at the beginning of this chapter. Thus a lack of drop in performance at extremes of laterality could be dismissed as the consequence of using a practised measure like box-marking. However, the unpractised measure of match-picking shows little in the way of a consistent drop-off in cognitive performance at extremes either. Ultimately, this could be dismissed from the factor analysis literature, as there are many potential measures of laterality, and the one preferred by Annett is neither of the measures here. Perhaps refutation of 'heterozygote advantage' should be left to analyses of peg-boarding (eg. Mayringer & Wimmer 2002).

The Annett Right Shift theory has been extended to account for schizophrenia (Annett 1999), suggesting that individuals with schizophrenia have the RS+ gene (a right shift gene, impairing the right hemisphere) and an agnosic gene impairing the left hemisphere (which will occur in 50% of individuals with an agnosic gene). The prediction is therefore of decreased asymmetry, and decreased function overall.

The 3D figure for schizophrenia supports a decrease in language function, but it again must be noted that the figure shows a decrease in laterality for cases of schizophrenia as a group, but not for individuals themselves. There is no evidence here of restriction on hemispheric development imposed by a gene on any given individual. The variation in group laterality is a consequence of the distribution of the sign of the laterality. Thus, laterality as defined by absolute ability on the box-marking task does not support that prediction.

Conversely, if the restriction is seen as having an effect on side of handedness only, the findings do support the hypothesis. Again, the theory is unable to make predictions that are specific enough to test.

Overall, I would conclude that the Annett Right Shift Theory is not supported by the data in this three-dimensional analysis, on the grounds that it proposes a restriction in hemispheric development, not merely control over side of speech or hand dominance.

THE MCMANUS "DEXTRAL ALLELE" THEORY

The McManus theory (1985 monograph) does not propose, and therefore does not predict any link between cognitive function and the dextral allele. Thus it suggests there will be no correlation between binary handedness and cognitive function, a finding well born out in the literature. Accounts of mixed hand preference (and less functional asymmetry) and poorer cognitive function can be understood in terms of associations between mixed hand preference (and less functional asymmetry) and handicapping conditions.

It has been argued above that the 3D figure suggests that poorer cognitive performance is associated with loss of asymmetry for all levels of absolute performance. This, as discussed above, remains compatible with a more general notion of 'handicap', associated with poorer function and decreased functional asymmetry, which will be a characteristic of laterality in unimanually practised measures anyway. Thus the findings can be interpreted as supporting this hypothesis as well. Perhaps this just illustrates the difficulty in making a testable hypothesis from mechanisms that are themselves derived from all the available empirical evidence.

The findings support a continuous association between degree of lateralization and cognitive function. This might be felt to go against the spirit of the McManus theory, but strictly, as this theory covers handedness sign and not degree, it should perhaps more properly be concluded to be agnostic regarding these findings.

THE CROW HYPOTHESIS

The Crow hypothesis is that psychosis is a component of the variation associated with the evolution of the Homo sapiens-specific capacity for language. The capacity for language it is proposed arose from a genetic change that allowed the brain to lateralize. The variation in trajectory of brain development intrinsic to this change includes a component that represents the predisposition to psychosis.
Thus variation in the development of lateralization would be anticipated to be a marker of individuals predisposed to psychosis. It is not specified, therefore, exactly what differences will be seen, beyond their being differences in some aspect of lateralization. Does this analysis add anything that may be testable?

The data presented are relevant to this theory. Firstly, there is support in the 3D figure for linking lateralization and cognitive performance. If this model is rejected, some other explanation is needed for the association seen. Secondly, most of the population is more lateralised than the optimum for hand skill. Box-marking thus may be taken as an indirect index of lateralization for the more fundamental variable of language. According to this view there is some evidence from box-marking (as also from hand preference data in the NCDS dataset, and other sources - see Sommer et al 2001) that those who in adult life develop schizophrenia are less lateralised than the population as a whole.

It should be noted that the original observation of decreased functional lateralization of the premorbid schizophrenia group was originally made in this same dataset; that there is support for the hypothesis is therefore not surprising. The question is whether this approach has added anything.

The three-dimensional plot puts the differences in laterality and function in the context of the normal population. For example, a distinction can be drawn between the bulk of the cases, whose individual lateralization is normal, but who as a group have a relative excess of left-superior individuals, and the group of aberrant 'low performers' which appear to have decreased laterality as individuals. This seems finer-grained information than just lumping the two changes together as 'a decrease in laterality'. This apparent heterogeneity is not apparent from a two-dimensional plot of laterality versus caseness, for example.

If the loss of asymmetry is seen solely in terms of a loss of the bias in distribution of the 'sign' (R or L), the box-marking measure certainly demonstrates a loss of this bias in the cases of pre-morbid schizophrenia. This is an important conclusion; the mechanism whereby a function is restricted to one hemisphere is unilateral; the alternative pathological situation, where the bias is not operating, is an equal distribution to the right or left. The biasing factor does not necessarily encourage increased lateralization, it merely encourages lateralization to a particular side.

The clear loss of asymmetry is found in the group of cases as a whole. The general direction of the effect is compatible with the hypothesis. For the majority of cases there is a small cognitive deficit, normal degrees of lateralization, but a loss of the right-superior population bias. If we take the box-marking laterality as a proxy for language laterality, it is then clearer that the primary deficit in schizophrenia is a loss of a population bias for locating speech in the left hemisphere.

We can pursue this assertion in the emerging literature on functional imaging of language. For example, Sommer Ramsey & Kahn (2001) have demonstrated an apparent decrease in language lateralization in patients with schizophrenia. Activation in patients is prominent in both hemispheres, rather than just on one side as in normals. It is an effect in individuals, not just in the population.

The Crow Hypothesis is hazy on exactly what it predicts, beyond individuals with schizophrenia showing evidence of disordered lateralization of function. We would have to propose that whatever alters the distribution of hand superiority for box-marking is also altering the lateralization of language function in individuals. One effect appearing in these two areas of function, altering the degree of lateralization of one function (language) in *individuals*, and the overall direction of lateralization of another (superiority at box-marking) in *the population*. This might be understood as an early effect on hand preference and a late effect on language development, the difference then how noisy a correlate each is of the underlying lateralising mechanism.

However, at present no mechanism for mediating these lateralization differences is being proposed. Thus this presentation of the data can simply be said to support the Crow Hypothesis by addressing the McManus question of handicapped groups, as well as allowing examination of the performance and lateralization of premorbid cases of psychosis in the context of the general population.

The Thesis Defended?

With reference to the explicit aims highlighted in Chapter 4:

1. The analyses presented in this thesis clearly demonstrate that plots of performance against laterality of that performance are highly misleading. This has resulted in an erroneous view of the relationship between performance and laterality that underpins one of the most influential theories about the origin of handedness, the Annett right-shift theory. It is clearly not true to say that figures of this sort presented both here and by Annett show restriction of the non-dominant hemisphere.
2. Unlike the analysis using laterality indices, the analysis of cognitive performance and laterality in three dimensions has clearly demonstrated that the handicap around symmetry is not due to over-representation of handicapped individuals around

symmetry, as suggested by McManus, but rather that this is a characteristic of the population.
Thus, the thesis is defended.

Future directions

The need to focus on what is being explored & why.
A large quantity of work now confirms qualitative losses in asymmetry in a variety of illness groups. The wide variance in these measures suggests that the focus should move from testing enough individuals to measure the sign of an effect, to testing enough individuals to measure the size of effects. That there are differences eg. in individuals with schizophrenia is now accepted (Sommer et al 2001), and what is perhaps more striking than a certain test's sensitivity to these effects, is that almost any continuous test shows a loss of asymmetry in schizophrenics.

But there is a cautionary tale in chapters 8 & 9 of this thesis. Slightly different measures can show very, very different relationships to brain function. The effects of practice, and the potential circularity of arguments surrounding this, have also been discussed. The final conclusion could be that the relationship between cognitive function and hand skill for box-marking is just more readily-explained than that for match-picking. It has been argued that variables are more interesting (in the sense of probably having something to do with the distribution of writing hand) if a significant proportion of their variance can be accounted for by preferred hand for writing. But this is only true if one believes there to be a connection.

The other emphasis has to be on clarifying those aspects of development that are responsible for differences in lateralization of function. Functional imaging is contributing to our understanding of how tasks are lateralized in the brain, which in time may lead to an understanding of how and why this affects function ie. connecting up the central axis of the map in chapter 4.

Clarity is needed about how lateralized processes develop in the brain and how we can measure this, rather than just qualitative statements about there being more or less 'laterality'. The orthogonal nature of the laterality derived from many measures available bilaterally suggests focus is needed on how we think these differences develop, rather than just measuring things because we can.

The need for statistics
What is needed next is a hypothesis about the size of any effects one might see in three dimensions. For example, the steepness of the notional planes seen, and from what direction. At present we can merely examine their gross form, rather than exploring how big and how significant any deviations from a flat plane. We can generate 3D 'confidence interval planes' in a similar manner to the confidence intervals seen in 2D in the lowess figures (page 121), although these will only tell us the significance of deviations from a flat plane. Predictions could be made about the steepness or shape of the valley sides from models connecting one-sided practice to function, and these could then be tested with respect to the data presented here.

In pursuit of the effects of practice

An interesting experiment, in pursuit of the suggestion (above) that practice may mediate both cognition and lateralization, might be to take subjects that have performed a supposedly ‘un-practised’ task (eg. peg-boarding, match-picking etc.) and get them to practice with their preferred hand. Although the practice is taking place in a very different epoch neurodevelopmentally-speaking to that in which preferred writing-hand practice occurs in most individuals, one would expect to see the two sub-populations (by preferred hand) separating, and a dip in cognitive function around zero develop, to resemble the box-marking results.

Correct modelling of fecundity measures.

The analysis of numbers of children in chapter 9 was technically deficient, and included merely as an illustration of the visualisation technique; strictly one should not attempt estimation of the central tendency of the number of children using a simple calculation of a local mean. Extending the analysis to estimate a negative binomial distribution would be more correct, and allow estimation of a true effect size, and variance. This relationship, central to notions of fecundity, may be key in any genetic model.

Sex differences

Figure 24 in chapter 8 does suggest that sex-differences are readily-visualised in this way. Further exploration of these interactions is desirable while the question of genes controlling lateralization being located on sex chromosomes remains.

Changes over time

We have examined adult outcome with respect to hand skill at age 11. It would be very interesting to know what happens to relationships between cognitive function and measures of laterality, throughout development.

Effects of 'the chirality of cognition' on preference measures

The finding mentioned in chapter 2, that preferred hand influences recall of sided information, suggests an investigation of the size of this effect in relation to the commonly-asked components of preference scales - to what extent are preference scales confounded by this? One could also take heed of the warnings about the 'ethological validity' of many lab measures of handedness, and, for example, attempt an assessment of hand preference in a variety of real-world situations using videotape analysis.

Latent class modelling of this data - in search of 'laterality'

Recent developments in structural equation modelling have made it possible to mix a variety of different manifest and latent variable types (eg. categorical preference and continuous performance). With the large number of subjects and different measures over time available in the cohort data, it may be possible to model 'underlying laterality', and effects of hand preference and sex on this, despite the considerable variance in the data. Such a model may then provide predictors that could be explored in individual subjects.

Is there a '10% rule'?
Neural network models already hint at an 'optimum degree of lateralization'; the hand skill vs. lateralization findings put a number on this. Pursuing this notion in other large datasets, would be interesting. The question has already been raised whether the difference between the population mean laterality being greater than this points to another function, more selected for than hand skill, that has a '16% rule'; verbal skill 'by side' estimates from functional imaging might provide a way in to this.

Data from other cohorts
Given the unsatisfactory conclusion here (that the 'most informative' meaure is not one we have in both cohorts), it would be highly desirable to reproduce the basic shape of the verbal surface from a suitable test in another dataset.

3D - A technique that can generalise?
The need to present data with respect to two, and not one, independant variable (measures on R and L) is fairly unique. Apart from spatial analyses, there are few situations in which one can put variables on the X & Y axes that are so independent, yet so similar that the notion of '2D performance space' appears meaningful. This interchangeability of the two axes serves as a warning of the novel nature of the distinction being made between the two variables, both hand performance, 'merely' one on the right and one on the left. This raises the possibility that the 3D techniques developed here will not prove generally useful, at least in epidemiology.

Nevertheless, there may be other areas where the communication of this extra dimension will of itself inform, as well as obviate the need to reduce multivariate entities to single, potentially-misleading indices. When initially exploring data, there are times when increasing the dimensionality of ones' scrutiny, rather than reducing it, usefully changes the perspective. A circle becomes a sphere, and the penny drops.

Chapter summary
The field of laterality research faces many hurdles, in the areas of conceptualisation and understanding aetiology, similar in some ways to the difficulties facing researchers into schizophrenia. A century of scientific enquiry on a 'primary measure' remains elusive, and a morass of measurable outcomes threaten to bury rather than illuminate.

Performance measures in laterality research consist of two measures, one from each side, and how this data relates to notions of 'laterality' depends upon how this is conceptualised. The 'fog' surrounding laterality indices have led to some spectacular misunderstandings about the nature of the relationships between performance and lateralization of that performance.

However, the bivariate construct of measurements by side can readily be appreciated and visualised in relation to a variety of other outcomes. Using a bivariate approach avoids the confusion and opacity brought to the field by the use of laterality indices.

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APPENDICES

Appendix A

Notes on examples of lateralization

(1) Physics.

Shortly after the Big Bang, colossal amounts of matter and antimatter annihilated each other, releasing colossal amounts of energy. There was a minute excess of matter, however, infinitesimal leftovers that now make up the physical universe. It is possible to create and observe the partner particles (antimatter) in large particle accelerators, and they are observed behaving exactly as matter does, but having opposite charge and symmetry. For example, it is known too that certain subatomic particles called neutrinos are only encountered spinning clockwise, so-called 'lefthanded' spin. Spin in the opposite direction is observed in their antimatter equivalents only.
Thus there is apparent symmetry and asymmetry in nature at the most fundamental level, although one could criticise this observation on the basis that it is actually the concept of symmetry that is a basic building-block of western scientific philosophy, rather than vice-versa.

(2) Chemistry.

Most amino acids are geometrically 'chiral' (adjective "Asymmetric, not superposable on its mirror-image"), and the amino acids used by living organisms are all 'levo' ie. their kinks are left-handed, and they only interact with other 'left-handed' proteins. There is thus a profound asymmetry to the chemistry of life, with right-handed amino acids being excluded. The chirality is a consequence of their complexity and geometry in 3 dimensions. We can only presume that whatever chance processes resulted in the origin of life involved left-handed proteins. Right-handed proteins were abandoned on the platform as the locomotive of life departed, in an extreme act of natural selection. It is not generally thought that this L-form amino acid preference is a consequence of one 'handedness' being functionally superior. Right-handed amino acids appear to behave in identical ways (with each other) to left-handed ones. Thus it seems unlikely that the 'choice' of left-handedness was a consequence of some more fundamental quality of matter, such as the asymmetry of neutrino spin.
On the other hand, some researchers have suggested the L-form preference is a consequence of the fact that bombardment of L & D amino acids by 'lefthanded' neutrinos leads to differential ionisation of D forms, thus favouring L. However, given the ubiquity of lefthanded neutrinos this theory of the origin of the L-form preference would seem untestable.

(3) Biology.

As with any phenotype under selection, there is insufficient variation in the chirality of proteins to explore whether they in any way dictate asymmetry in organisms. Once more, the existence at the larger scale of both forms of structural 'handedness' in all fields of biological development suggests this is not the case.
However, L-amino acids form right-handed alpha-helices, and these proteins consequently form left-handed superhelices. Thus structures on opposite sides of a symmetrical structure would twist the same way, rather than demonstrate symmetry. The helical structure of flagella and cilia build up in this way, resulting in bronchial cilia beating in the same direction. When this co-ordinated pattern is absent eg. in Kartagener Syndrome, dextrocardia or situs inversus can occur, suggesting that macroscopic symmetry may be being biased early on by microscopic asymmetries.

[4] Organisms.
Single-celled organisms are internally asymmetrical, and the arrangement is passed down through the generations. Unicellular ciliates swim by rotating in only one direction, and even amoeba will swim around a glass rod more frequently in one direction than another (Schaeffer 1928).

[5] Invertebrates.
Right/left asymmetries exist in invertebrates. In sea urchin embryos, right and left-sided physical asymmetries have been shown experimentally to depend on the orientation of their dorsoventral and anteroposterior axes (McCain & McClay 1994). This can be seen as very similar to our own perception of right & left with respect to our head-foot and front-back axes.

[6] Vertebrates
Origins of their bilateral symmetry: In nature, cells can replicate and form structures in chains (1-dimensional), sheets (2-D) or clumps (3-D). Multicellular organisms initially develop as clumps of cells. However, what happens in many cases (eg. vertebrates) is that at some point a gap or lacuna forms in such a clump, leaving a layer of cells between the 'inside' and 'outside'. This layer can then be considered a sheet, ie. can be perceived as a 2-dimensional object, even though in practice it has depth as well. These functional sheets place us briefly back in 'flatland', in which any geometry viewed side-on looks like a line.
Cells at the centre of the sheet experience a different environment from those at the periphery. Any differentiation reflecting this difference in environment can result in different chemical messengers being released by the cells, setting up a concentration gradient between the centre of the sheet and the edges. What then appears to happen is that, somewhere along the edge of the sheet, a signal of some sort (in chick embryos, gravity, in most species, as yet undetermined) causes cell differentiation. This differentiation can then follow a concentration gradient which will exist between the edge and the centre of the sheet. In this way, a line of differentiation is formed, a midline of the embryonic creature (Gilbert 1997. p.238). Any cell in the sheet can then be orientated, in terms of distance from this lines, as well as orientation along the gradient/line itself.
Once the midline is established there will be two positions, at the same position along the line and equidistant from it, that share the same conditions. Hence a reflected symmetry will be seen in any structure that develops using this coordinate system. The perceived symmetry will derive from a lack of differences in the conditions, rather than one side having any 'awareness' of what is happening on the opposite side. Further differences can then develop in relation to this line, which in the absence of asymmetrical conditions will appear reflected across this line, thus demonstrating apparent bilaterality. It is easy to forget that the empirical observation of bilateral symmetry in nature does not imply causal links between each side, beyond a likelihood of a common origin.
Any vertebrate is a development of flat sheets of cells developing midline ridges; the rest follows. This includes the right and left lobes of the brain and the extremities, which are anatomically identical. Unbalanced use of the extremities could result in different sizes for their musculature, muscle attachments etc., but in the case of the human, hand anatomy remains so similar on each side that hand preference cannot be determined post-mortem.

[7] Linked asymmetries
It should not be overlooked that asymmetry in one area may develop not through selection for that feature, but through selection for another feature, whose subsequent asymmetrical development leads to asymmetry in the first. In theory, asymmetry on one region of the brain could lead to a mixture of growth and/or suppression locally and/or distally (Geschwind & Galaburda 1987). In developmental terms, the 'primary' asymmetry might be seen developing first, but the final decision about which asymmetry is primary and which secondary would rest on the hypothesis under test, as with all evolutionary biology. Indeed, the notion that asymmetries develop singly seems unlikely. The 'linked asymmetry' argument has been extended into the suggestion that hand skill is favoured on one side purely due to the proximity of the relevant motor cortex to Broca's area, and it is this latter brain area whose asymmetrical growth is most clearly being stimulated by some unknown factor.

[8] 'Basically symmetrical' or 'basically asymmetrical'?
All vertebrates demonstrate clear structural bilateral symmetry, so the focus will now be on deviations from this. Although not all species have been studied, there are probably clear asymmetries in all vertebrates; the vertebral column provides an axis of symmetry, and the smallest deviation from a mirror-image could be considered asymmetry. In the more complex vertebrates it is the internal arrangement of organs that is most obviously asymmetrical. The external appearance preserves the sense of structural symmetry. Functional asymmetry is also common, although the status of population-level asymmetries is less certain (McGrew & Marchant 1997).

[9] Lobster claws.
Lobsters often have one large 'crusher' claw on one side or the other. This larger claw develops as a consequence of exposure to more oyster shells than on the other side, and 'exposure to oyster shells' being randomly-distributed there is an equal distribution of 'crusher side' in the lobster population (see review in Geschwind & Galaburda 1987).

[10] Fluctuating asymmetries.
The biological substrate for asymmetry consists of differentiations from a 'midline' which, however real, is not a mirror. Biological noise (environmental differences by side) will result in small differences between sides called 'fluctuating asymmetries', and these will of themselves be distributed 50:50 in the population. Any parts of an organism that would otherwise develop identically will exhibit these differences. This noise might even 'drown out' a systematic difference between the sides measured in a population. It cannot be argued that these 'fluctuating asymmetries' provide the starting-point for any selection of asymmetries, as they are not a consequence of gene expression. Nevertheless they can be invoked as the origin of any asymmetry that is distributed 50:50 in a population. This can apply to both structural and functional asymmetries.
Even this argument assumes symmetry to be the norm, and must be placed in the context of the enormous variety of population asymmetries present at so many levels in nature. The bilateral symmetry of vertebrates is in contrast to these. From a world of asymmetry, vertebrates have developed with a remarkable degree of structural symmetry. Measurable performance advantages in unilateralism seem balanced against theoretical survival advantages in bilateralism.

Appendix B

One gun or more?

The development of battle tanks flirted briefly with multi-turreted machines, each with its own operator. For example, the Russian K-35 heavy tank designed in the late 1930's had 5 turrets. However, aside from issues of size and reliability, it became clear that such machines lacked tactical flexibility over their single-turreted counterparts. In summary:

"1) The turrets, apart from the main turret, did not have 360 degree traverse , and therefore were tactically limited.

2) Such turrets added to the cost, complexity, crew numbers, weight and maintenance problems of the tank, and impaired its manoeuvrability, without adding to its fighting power.

3) Secondary turrets could not be heavily armoured, were excellent "shot traps", and increased the vulnerability of the tank to AP shot penetration, and internal explosions from stored ammunition.

4) Secondary turrets restricted the diameter ring of the main turret, which was incapable, therefore, of being up-gunned."

[ref. Dr John Bullen, Imperial War Museum, personal communication]

It was rapidly appreciated in the crucible of the Second World War that a tank is most likely to survive if it has a single turret with a single large-calibre weapon, and this pattern is still preferred today.

Appendix C

The Mirror paradox
Confusion easily arises with structures that seem to have such an 'intuitive' quality to the origins of their bilaterality. Two sides, or even two axes, can appear very similar, and yet be fundamentally different, independent of each other. For example where a limb fails to develop on one side development on the other side can appear completely normal - although in the normal state there is symmetry, there is not necessarily any interdependence. The two sides develop as mirror images of each other in complete ignorance of each other, but we readily jump to conclusions about causation.

A snare set by the 'intuitive grasp' of symmetry is the so-called "Mirror paradox". Looking at oneself in a mirror, it appears that while 'Right' is swapped with 'Left', 'Up' is not swapped with 'Down'.

It is not entirely obvious why this should be. When we look in a mirror our heads & feet are in the right position, but when the individual in the reflection moves their hands, they appear to move the 'wrong' one, the 'wrong' wrist has the watch on etc.

Up and down are more explicitly 'externally indexed' than left & right - we are not symmetrical in the up/down plane, and a horizon of some sort is seldom out of view. Our definition of right and left however is referenced to our vertical orientation and our direction of view. In the 'anatomical position' we stand up, and look forward, and it is from these references that we define our right and left.

So, we then look at ourselves in a mirror:
1. We're unlikely to confuse a head for a foot - up/down orientation is unambiguous.
2. Depth is reversed. This is not the axis in which we are confused here, although depth reversal can be confusing as well, as anyone who has attempted to tie a bow while looking in a mirror will know.
2. Sidedness, on the other hand, lacks such clear cues - our reflected selves' symmetry leaves few clues. When we move our left hand what we see moving is the 'right hand' of the reflected individual. Why?

Although there are other explanations, the effect can be considered as a consequence of the mental manipulation we perform; we 'take their place' to determine where (given their up/down orientation and the fact they're facing us) their right and left are. As mentioned earlier, real objects cannot reflect, they can only translate and rotate. If we were to remove the mirror and take their place, we would have to rotate. This would reverse our left & right. So what we do is misinterpret 'how they got there', and thus mis-identify their right & left.

Experiments with individuals wearing prisms etc. show that it does not take long for the brain/eye to adjust for reflection of the images seen. It is the physical impossibility of 'reflection' that fools us; rotation swaps R&L but leaves up & down intact.

Appendix D

Responsibility in the use of personal medical information for research. Principles and guides to practice. Statement by the Medical Research Council. Revised September 1994. Section 1 page 5-6.

"Consent to use personal medical information.
As stated above, the transfer of information from medical records for the purpose of research requires the consent of the medical custodian. Consideration has been given to the question of whether it also requires the explicit consent of the patient. Such a requirement would, on occasion, be likely to vitiate studies which depend on the completeness of samples of information on patients as, for a variety of reasons, it would not be practicable to seek the consent of each and every patient. Sometimes many thousands of patients are involved. Frequently, records must be included on patients who are unavailable or untraceable because of changes of abode, migration or death. In some research, obtaining consent may itself cause needless anxiety.
The Council therefore consider that, subject to scrupulous safeguards about confidentiality, information about patients can be properly available for medical research without their explicit consent, as it has been in the past."